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A Chemical Testing Support System (CTSS) recommended as one of the core components of the Chemical Substances Information Network (CSIN), would facilitate compliance with Federal government testing and reporting requirements, and would simultaneously provide a sophisticated mechanism for the analysis of animal testing data. In a survey of existing systems, attention focused on the Toxicology Data Management System (TDMS), which is a prototype, automated system for the conduct and evaluation of laboratory animal experiments. The report outlines an implementation scenario for incorporating CTSS requirements into the TDMS.

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FOR A
CHEMICAL TESTING SUPPORT SYSTEM

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EXECUTIVE SUMMARY

A Chronic Testing Support System was recommended in the Mitre Report as one of the core components of the Chemical Substances Information Network (CSIN). Under a contract with the Council on Environmental Quality and the Information Exchange Group of the Interagency Regulatory Liaison Group (IRLG), Sigma Data has conducted a study of the general design requirements for implementing a Chemical Testing Support System (CTSS). (Because users indicated early their interest in acute as well as chronic studies being available within a single system, "chronic" was changed to "chemical.")

The potential user requirements were assessed with particular emphasis on those of the Office of Toxic Substances within the Environmental Protection Agency because of its key role in the implementation of the Toxic Substances Control Act (TSCA). A CTSS would assist industry and private laboratories in complying with federal government testing and reporting requirements, and would simultaneously offer a sophisticated mechanism for the analysis of test data. Because standardization is imminent, and the volume of test data is anticipated to be high, an automated system was considered justified. Additional interest was expressed by all potential users for a test directory which would include all tests submitted by industry as well as those conducted by the government. Inclusion of tests in progress was also urged.

Existing systems fell into two categories: those pertaining to a directory of tests, and those pertaining to automated data collection and analysis. Several test directories were investigated which included tests completed as well as those in progress; however, a directory to the contents of a CTSS would be required, possibly through another component of the CSIN, or as a companion catalog file to the analytical test data. With respect to data collection and analysis, a joint effort between the National Cancer Institute and the National Center for Toxicological Research, has produced a prototype CTSS known as the Toxicology Data Management System (TDMS). TDMS provides the user with automated procedures throughout the course of an animal experiment including bioassay, protocol analysis, experiment information, and test data analyses.

The TDMS, an integrated, existing system, is recommended for the implementation of the CTSS because of its present federal support, the existing expertise in the collection and analysis of animal data, the prototype software for animal test data analysis, and its prototype network status. This report outlines a possible scenario for incorporating TDMS into CTSS. Full implementation of the TDMS will require at least two years, and full interagency cooperation and coordination can assist in the realization of that goal. Several key next steps are necessary:

- development of worksheets and machine-readable formats which conform to the IRLG Testing Standards and the TSCA Sections 4 and 5 testing and reporting rules

- designation of a contractor to develop the hard copy worksheets and machine-readable formats, and to write the necessary tape conversion programs
- use of Chemical Abstracts Registry numbers
- coordination with other Chemical Substances Information Network development efforts
- establishment of a formal relationship with the Laboratory Animal Data Bank (LADB) at the National Library of Medicine for the exchange of control animal data.

1.0 INTRODUCTION

1.1 Background

Until recently, Federal authority for protecting against hazardous chemicals was fragmented and inadequate. Several Federal agencies such as the Food and Drug Administration (FDA), the Consumer Product Safety Commission (CPSC), the Occupational Safety and Health Administration (OSHA), and the Environmental Protection Agency (EPA) have regulatory authority over the different types and uses of chemical substances. Federal laws which provide some of the authority for chemical regulation include the Federal Food, Drug and Cosmetic Act; the Federal Insecticide, Fungicide, and Rodenticide Act; the Occupational Safety and Health Act of 1970; the Consumer Product Safety Act; the Clean Air Act; and, the Water Pollution Control Act.

Based on the problems presented by toxic chemicals, a Council on Environmental Quality report identified the need for an authority to:

- Require testing of chemicals to determine their health and environmental effects
- Impose use and distribution restrictions on chemicals where necessary to protect the public health and environment
- Collect information on chemicals and establish a system for classifying and using such information.[1]

In order to close the gap and eliminate the deficiencies in various regulatory laws, the Toxic Substances Control Act (TSCA) was passed. TSCA provides EPA with broad powers to regulate chemical substances not covered by existing Federal regulatory authorities for the purpose of preventing unreasonable risk of injury to health or the environment associated with the manufacturing, processing, distribution in commerce, use, or disposal of chemical substances. Section 4 of the Act requires manufacturers and processors to bear the responsibility for adequately testing potentially hazardous chemical substances to determine their health and environmental effects. This section applies to all new chemical substances entering commerce as well as chemicals already on the market that are identified as potentially dangerous. Based on the evaluation of the test data, TSCA provides the authority to ban or limit manufacturing, processing, distribution, or use of chemicals and to specify disposal methods or warning labels when a chemical substance is found to cause, or significantly contribute to, an unreasonable risk to health or the environment.

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[1] CEQ, "Toxic Substances," 1971.

After TSCA was enacted, one of the initial actions taken under the Act was to fulfill Section 25 (b) which required the Council on Environmental Quality (CEQ), in consultation with other agencies, to coordinate a study of the feasibility of establishing:

- A standard classification system for chemical substances
- A standard means for storing and for obtaining rapid access to information related to these substances

The Mitre Corporation was contracted to conduct a feasibility study to determine user requirements and system development options for implementing the above criteria. The Mitre report (MTR-7558) recommended development of a Chemical Substances Information Network (CSIN) as a means of providing the necessary information to Federal agencies and others involved in the study and regulation of chemical substances. The CSIN would consist of a number of independent information systems or components: The components of primary importance would be considered "core components" which would be linked together either directly or indirectly.

One of the core components recommended in the Mitre report was a Chronic Testing Support System. The analysis of user needs indicated that a capability that stored and retrieved the results of chronic toxicity monitoring studies was required to adequately meet the requirements of testing and validation under TSCA and other federal laws.

The Mitre report indicated that a system with all these features does not currently exist but that the existing systems at the National Center for Toxicological Research (NCTR) and the National Cancer Institute (NCI) fulfill many of the requirements. The report recommended that a study be conducted to examine the feasibility of developing a Chronic Testing Support System that would incorporate the best features of the Carcinogenesis Bioassay Data System (CBDS) at NCI and the Automated Research Support System at NCTR.

In addition, the implementation of the Toxic Substances Control Act has focused attention on the overlaps and omissions in information collection and analysis of four regulatory agencies dealing with chemical substances (EPA, FDA, CPSC, OSHA). To coordinate research and regulatory priorities among the four agencies, an Interagency Regulatory Liaison Group (IRLG) was established. The IRLG was charged with:

> Examining the common requirements and functions of the four agencies as they pertain to the regulation of potentially hazardous and toxic substances and to begin a process by which present interagency cooperative efforts can be improved, augmented, or redesigned as necessary.[1]

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[1] Report on Progress of the Interagency Regulatory Liaison Group, July 1977.

The IRLG is divided into several functional work groups, one of which is the Testing Standards and Guidelines Work Group. This work group was established to develop common guidelines and criteria for testing chemical substances required by the four regulatory agencies. By developing compatible standards and guidelines, costly duplicative efforts would be avoided, and the comparison of like information among agencies would be facilitated. As a result, coordination and cooperation would be maximized to produce a sound, scientific base for regulatory decisions.

1.2 Approach and Scope

In the implementation of TSCA, EPA has assigned priority to the following activities:

- Establishment and implementation of a pre-manufacturing review system
- Establishment of initial testing requirements
- Promulgation of regulations to control some of the environmental problems associated with existing chemicals
- Assessment and control of unanticipated problems of immediate concern.

This study analyzes user needs, system design requirements and implementation options for the Chronic Testing Support System recommended in the Mitre report, and responds primarily to the first two priorities enumerated above. Whereas Mitre focused on a search and retrieval capability for the results of chronic toxicity studies, Sigma Data ~~proposes an expanded system to include~~ acute ~~and~~ subchronic tests. Thus, the system will henceforth be referred to as a Chemical Testing Support System (CTSS). The primary intent, however, of furnishing an automated system for the collection, monitoring, reporting, and evaluation of bioassay information remains unchanged.

The initial effort, with respect to both the information content (data elements), and the implementation (operational) design requirements, was directed toward the formulation of general system objectives. Interviews were conducted with personnel in the four primary regulatory agencies (EPA, FDA, OSHA, CPSC) as well as with selected representatives from the industrial community. The information obtained from these interviews was then used to develop a user needs profile. Sigma Data integrated these requirements with the existing capabilities and constructed a model for a proposed system divided into the following functional operations:

- Data collection
- Data submission
- Storage and conversion
- General inquiry
- Detailed analysis and evaluation

Based on the requirements of the proposed system, Sigma Data surveyed applicable existing capabilities to determine to what extent they could be incorporated into the CTSS. Considerable attention was focused on the Toxicology Data Management System (TDMS) at the National Center for Toxicological Research because it represents an integrated capability which closely approximates our initial conceptions for a CTSS.

Each of the functional areas noted above is examined both within the context of a completely integrated CTSS and as a distinct operational component. However, the general analysis must be viewed as comprising the following components:

A. SYSTEM DATA CONTENT and MANAGEMENT - What data or information should be collected and maintained within the system? This component of the analysis involves the following considerations:

   1. Specific data elements within the system
   2. Data collection methods
   3. Problems of standardization - nomenclature, reporting formats, etc.
   4. Data storage and management - usually refered to as Data Base Management requirements. It involves questions of editing, updating, simple retrievals, physical storage, security and confidentiality
   5. End Users

B. DATABASE ACCESS and ANALYSIS - What facilities should be available to the users for the retrieval of information and the analysis of the data contained within the system? This component involves the following considerations:

   1. Retrieval of information about the specific contents of the database, i.e., a directory of animal tests
   2. Retrieval and analysis of test data
   3. Types of analytical capabilities; simple summary statistics to detailed statistical analysis

The answers to these questions ultimately dictate what kind of system and operational facilities are needed to implement the CTSS. That is:

a) Should an existing system like TDMS be adopted for CTSS?

b) What type of data base management system is most likely to meet general inquiry and data analysis needs?

c) What type and size of operational staff must be established to maintain the system?

The design specifications presented in this report are not sufficient to actually implement the proposed system. However, they do serve as a guideline for cost and manpower considerations and form the basis for detailed design and implementation efforts.

2.0 USER NEEDS AND OBJECTIVES

2.1 System Objectives

Section 10 of TSCA directs EPA to design, establish, and coordinate an efficient and effective system for the collection, dissemination, and retrieval of toxicological and other scientific data which could be useful in carrying out the objectives of the Act. Based upon this mandate and the general recommendations of the Mitre report which supported the development of an automated retrieval system for such purposes, it is necessary to explore in greater detail what kinds of capabilities are needed. In turn, the requirements for the satisfaction of those capabilities have to be established. In order to properly and thoroughly assess test data as required by TSCA, the overall objective of the Chemical Testing Support System as stated in the Mitre report would be to:

> provide a computer utility for collection, monitoring, evaluating, and reporting of bioassay information. The system permits collection of data on chemicals and chemical preparation, the experimental procedures and test environment, the observation data and complete pathology reports on individual animals.[1]

A computerized system would enable agency officials to review and to evaluate toxicological experiments in a consistent and expeditious manner. To satisfy this overall objective, four requirements were identified:

- Collection of Test Data
- Monitoring of Experiments
- Reporting of Test Results
- Evaluation of Test Results

Collection of Test Data - Evaluation personnel have realized that the growing quantity of data supplied to support health and environmental studies is tremendous. Furthermore, data often are submitted in different formats. Even the type of information submitted vary from including animal-specific data to animal group data. It is obvious, particularly in light of the increased reporting requirements of TSCA, that standardized reporting formats for bioassay studies are essential.

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[1] Bracken, M., et al, Chemical Substances Information Network, Vol. I. McLean, Va: The Mitre Corporation, Metrek Division, June 1977. MTR-7558 p. 5-22.

The Food and Drug Administration published proposed Good Laboratory Practice guidelines in the Federal Register, November 19, 1976, as a result of deficiencies it found in the conduct of laboratory testing in both the private sector and in government. It is anticipated that adoption of these guidelines will "assure the quality and integrity of data, "(41 FR 51206). By establishing standardized data collection methods, the validity of test results would be enhanced.

Monitoring of Experiments - There are two compnnents involved in the monitoring of experiments. The first concerns an awareness of research in progress or completed investigations in order to curb duplication of tests as well as to foster the sharing of test evaluations. The second component enables the review of the progress of an experiment periodically in order to maintain quality control and to analyze preliminary results for abnormalities that would necessitate a change in protocol or design.

Reporting of Test Results - The IRLG Testing Guidelines will not only specify the types of test data to be collected, but also the charts, graphs, tables, etc., which must accompany data submission. Based upon these guidelines, a procedure for submission and an established format are necessary.

Evaluation of Test Data - In conjunction with the submitted test results and supporting documentation, the evaluation process may include intensive analysis of test data. The capability of independent examination and/or verification was therefore another objective.

2.2 System Users

Sigma Data identified and interviewed the personnel in the four regulatory agencies (EPA, FDA, OSHA, CPSC) to determine their user requirements in fulfilling the objectives outlined above. Since any developing system would also affect other organizations, particularly industry, comments were elicited from representatives of trade associations and an independent testing lab which conducts a large number of animal tests under government contract. Officials at government testing laboratories were also interviewed. These conversations helped Sigma Data to assess the requirements of a CTSS in the implementation of TSCA as well as other laws and regulations. (Appendix C lists the organizations and personnel interviewed in the course of this project.)

Because of the varying responsibilities and needs of the individuals interviewed, no single survey approach was considered appropriate. Instead, the following issues were explored:

- Collection of Test Data
    - standardization of testing requirements
    - inclusion of control animal data
    - adherence to test protocols, present and planned methods of collection
    - monitoring of animal experiments
    - volume of test data
- Reporting of Test Results
    - inclusion of detailed test data
    - inclusion of summary reports
    - need for hard copy and machine-readable data
- Evaluation of Test Data
    - volume of test evaluations
    - estimate on turnaround time required
    - need for comparative analyses

2.2.1 Environmental Protection Agency

The two EPA offices primarily concerned with animal toxicological experiments are the Office of Pesticide Programs (OPP) and the Office of Toxic Substances (OTS).[1] OPP is responsible for registering, classifying and approving pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Before a pesticide is approved, an applicant must provide data regarding its composition, efficacy and hazards posed by its intended use(s). OPP must provide guidelines specifying the kinds of information which will be required to support the registration of a pesticide. The guidelines include standards for acceptable testing and the information required in test reports. These guidelines encompass three major areas of OPP concern: efficacy, human safety, and environmental safety. The human safety aspect is concerned with several types of human and animal toxicity studies: acute, subchronic, chronic, mutagenic, and special tests.

OPP requires supporting data from these experiments in order to judge the acceptability of registration of pesticides for their intended use. The supporting information includes chemistry and hazard evaluation. The hazard evaluation data are divided into wildlife and aquatic organisms, and human and domestic animals. Data collected by industry (raw and summarized data) are sent to the Toxicology Branch of the Registration

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[1] OPP will eventually be fully merged into OTS.

Division for evaluation. Due to the large number of submissions and the limited number of review personnel, most evaluations are done by analyzing the summary data. If a discrepancy is found, or a serious question arises, the detailed data are used for an in-depth review. The statistical analysis is conducted without the aid of a computerized system. The evaluation of a test may take from 204 days or longer. If it should uncover a possible hazard to human or animal health, the registration submission is sent to the Office of Special Pesticide Review (OSPR). OSPR is responsible for gathering and disseminating to other OPP branches information concerning tests that have been conducted for certain chemicals or classes of chemicals. The office indicated that a directory or catalog of tests would greatly facilitate that procedure.

The Metabolic Effects Branch of OPP is responsible for reviewing and evaluating the test data gathered by OSPR. In most cases the evaluation of a test includes investigating the detailed test data, which is currently done without automated support.

If sufficient evidence is discovered that indicates a potential hazard to human or animal health, a Rebuttable Presumption Against Registration (RPAR) is published in the Federal Register. The RPAR presents findings of the OSPR group and includes supporting graphs, charts, tables, statistics, etc. According to the Criteria and Evaluation Division and the Metabolic Effects Branch, they rely on the information supplied to them from OSPR. Because OSPR focuses particularly on positive results from a toxicity test, they may de-emphasize the negative results, thus creating a built-in bias. The feeling was expressed by the different evaluation divisions that an awareness of both kinds of test results would be of great assistance.

The Office of Toxic Substances was established to implement the requirements of the Toxic Substances Control Act. Section 4(b) of TSCA requires that EPA/OTS develop standards for the development of test data, testing methodologies, and the period of time within which the testing results shall be submitted to EPA. The testing rule may require submission of preliminary data prior to that of the final data. EPA may check to ensure that the testing data is developed in a reliable and competent manner in compliance with the testing standards. (Section 4(b) (2) (A) indicates that standards should be developed for animal tests, environmental effects, and chemical fate.)

The Office of Testing and Evaluation (OTE) of OTS will use several mechanisms for identifying hazardous chemicals including priority chemicals recommended by the Interagency Testing Committee (ITC)[1] and reports submitted under

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[1] The ITC was established under Section 4 of TSCA which authorized the formation of a committee to recommend to the EPA Administrator priority chemicals which might require a testing rule.

Section 8(e) of TSCA (notice of substantial risk) and Section 5 of TSCA (premanufacturing notice). OTE hopes to broaden the scope for the identification of hazardous chemicals as procedures are better refined.

Within OTE three divisions review effect and exposure data: Assessment Division, Health Review Division, and Environmental Review Division. Excluding pesticides, it is anticipated that 300 premanufacture notices for new chemicals will be submitted to OTE under Section 5 of TSCA annually, and that 50-100 studies will be required under Section 4. Considering the careful analysis and evalution which is needed, standardized report formats will be invaluable and automated techniques will be almost indispensable. (A brief outline of the chemical review process within OTE appears in Figure 2-1.)

The Interagency Testing Committee is responsible for recommending chemicals for testing to the EPA Administrator that might pose a potential hazard to human health or the environment and which need further testing. The Office of Testing and Evaluation will be responsible for requiring testing of these substances and for evaluating the results to determine the extent to which these substances are dangerous: i.e., conduct a risk assessment. OTE will be responsible for developing guidelines for conducting animal testing, specifying who should conduct the tests, monitoring the progress of the tests, receiving the results, and conducting an independent evaluation of the test results. Thus, use of a CTSS in these activities would facilitate test data evaluation to a great degree.

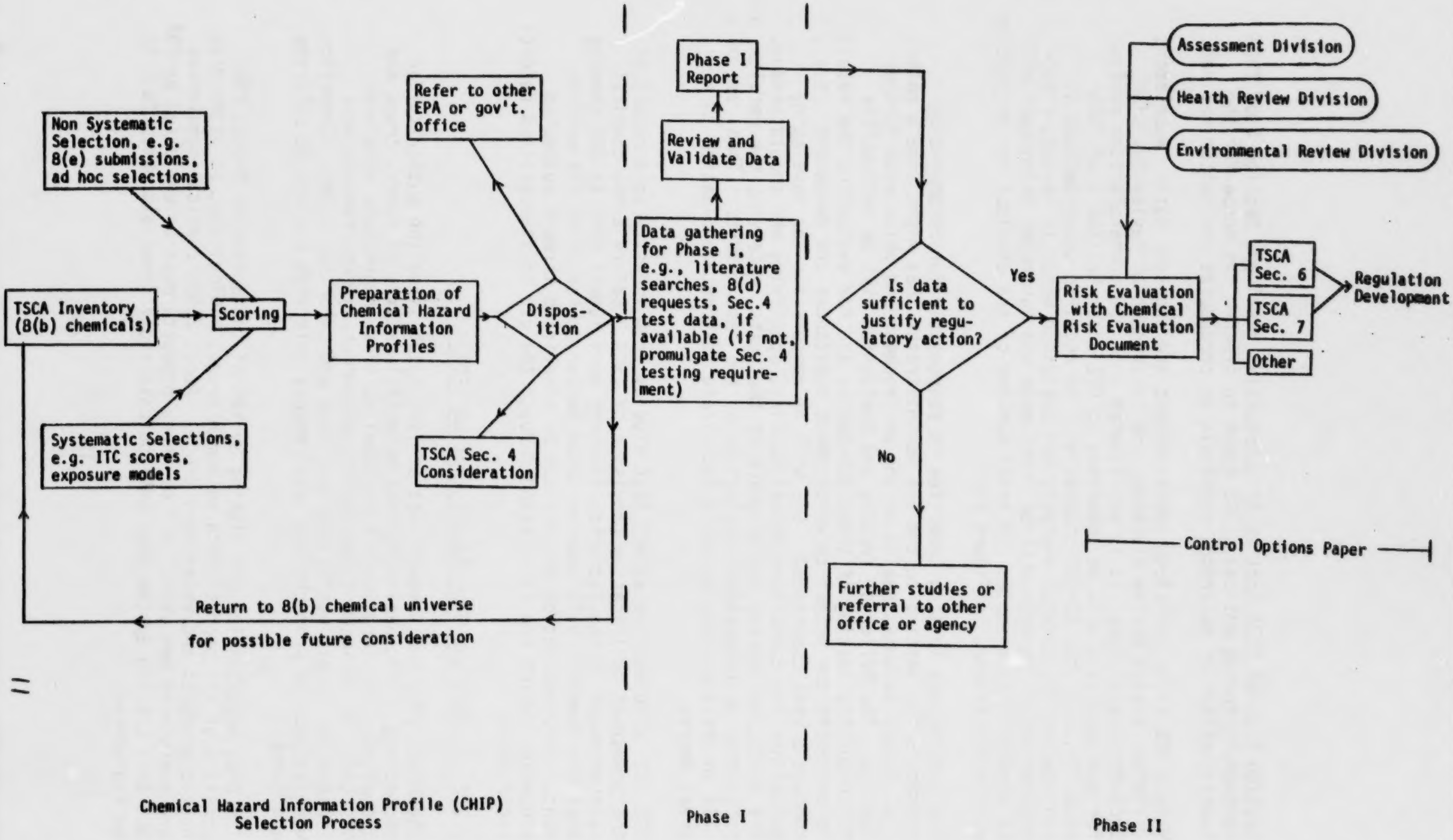
OTE will also receive animal test studies from industry as a result of the premarket notification provision of TSCA. Before a new chemical substance can be manufactured, industry must submit data to EPA showing that the chemical will pose no undue danger to health or the environment. This evaluation process can be simplified through automated procedures which are facilitated through the use of standardized reporting formats.

2.2.2 Food and Drug Administration (FDA)

The Food, Drug and Cosmetic Act of 1906 established the authority for protecting public health against potential hazards of foods, drugs and cosmetics. Adulterating and mislabeling of such products were prohibited. In subsequent amendments, premarketing requirements were imposed for drugs, pesticides, and food and color additives. Cosmetics were subject to premarketing requirements only with respect to coloring additives.

The Drug Registration and Listing System of the Bureau of Drugs, FDA, consists of all product data on human drugs, biologicals, in vitro diagnostic products and veterinary drugs. About 2,500 chemical substances are registered per year. All of these products must be evaluated by FDA but this Listing System does not indicate those chemicals which fail to be registered.

Figure 2-1 Chemical Review Process within the Office of Testing and Evaluation


Non Systematic Selection, e.g. 8(e) submissions, ad hoc selections
TSCA Inventory (8(b) chemicals)
Scoring
Systematic Selections, e.g. ITC scores, exposure models
Preparation of Chemical Hazard Information Profiles
Refer to other EPA or gov't. office
Dispos-ition
TSCA Sec. 4 Consideration
Return to 8(b) chemical universe for possible future consideration
Phase I Report
Review and Validate Data
Data gathering for Phase I, e.g., literature searches, 8(d) requests, Sec.4 test data, if available (if not, promulgate Sec. 4 testing requirement)
Is data sufficient to justify regulatory action?
Yes
No
Further studies or referral to other office or agency
Assessment Division
Health Review Division
Environmental Review Division
Risk Evaluation with Chemical Risk Evaluation Document
TSCA Sec. 6
TSCA Sec. 7
Other
Regulation Development
Control Options Paper
Chemical Hazard Information Profile (CHIP) Selection Process
Phase I
Phase II

Presently, for drugs, food additives, and color additives, the law requires manufacturers to file a petition seeking a use-granting regulation from FDA. The burden of proof of safety rests on the manufacturer. FDA reviews data submitted by the manufacturer and may issue an order specifying the ways in which the substance may be used, if at all.

All data collected by industry are submitted in hard copy. FDA, Bureau of Drugs, did attempt to accept computer tape support data, but there were too many complications with the wide range of computer systems used, and thus tape specifications were too complex to standardize. This data submission alternative was therefore quickly cancelled. To conduct certain analyses, however, a sample of selected data may be converted to machine-readable form, appropriately analyzed, and then erased for reasons of security as soon as the evaluation is completed. Otherwise, data are reviewed by non-automated procedures.

Within the Bureau of Drugs, there are teams of chemists, pharmacologists, biostatisticians, medical officers, and others who review petitions for New Drug Applications (NDAs) and Investigational New Drugs (INDs). Each reviewer has different information needs in assessing the test data submitted with drug applications.

One of the problems confronting the Bureau of Drugs is maintaining confidentiality of all test data submitted. Even after the drug has been approved, the data remain confidential. This is not the result of FDA policy, but rather stems from statutory law. Congress may change the law this year, but at present, the Bureau of Drugs is prohibited from contributing to a directory of test data.

On the other hand, FDA's Astro-4 Drug Information System collects data on NDAs and INDs. The data include the manufacturer, drug names, usage, pharmacological activity, route of administration, and the status of the drug application. No confidential information is contained in it.

There are two uses of a directory which would assist the Bureau of Drugs. In the course of the evaluation/review process, it would be valuable to know generic or trade name products chemically similar to the one being considered, and the related test data information. The Division of Drug Experience, which monitors the adverse effects of drugs, would be interested in the toxicological effects of chemicals, particularly in the areas of drug-food, drug-pesticide, and drug-general chemical interactions.

The Bureau of Drugs indicated that the resources at NCTR were not extensively used. NCTR focuses on longterm feeding studies and conducts few acute toxicity experiments. Priority lists are submitted by FDA to NCTR, but the latter has the right of selection and it is felt that this procedure has not been responsive to FDA's needs.

FDA does maintain several of its own animal testing laboratories. However, there is substantial contracting of experiments, particularly to university-affiliated laboratories. For the most part, the government laboratories' responsibility is to confirm test data submitted by industry.

FDA iterated that the evaluation machinery within the agency has not kept pace with the increased requirements for the reporting of test data. While the volume of test data has grown substantially, as has the number of chemical substances developed and submitted for registration, there has not been a corresponding growth in the personnel or resources allocated for such evaluation.

It may be concluded that FDA would benefit from the submission of standardized reports in a machine-readable format to facilitate product evaluation and registration.

2.2.3 Occupational Safety and Health Administration (OSHA)

The Occupational Safety and Health Act of 1970 authorized regulation of the workplace environment. Several specific functions included in that Act were the establishment of occupational safety and health standards; the enforcement of such standards; and the provision for research related to occupational safety and health.

In order for OSHA to develop regulations, it must depend upon the "best available evidence" which results from research demonstration, experiments and other appropriate information (84 Stat 1594). Sections 20 and 21 delegate responsibilities to the National Institute for Occupational Safety and Health (NIOSH). The research programs conducted by NIOSH may be done at their own initiative or at the request of OSHA.

At hearings on proposed regulations held by OSHA, industry may submit test data to support their assertions with respect to health and safety. OSHA has expressed a strong interest in developing the capability of evaluating these test results. The agency expressed a need for the technical support to defend proposed regulations without having to depend upon the expertise of other agencies.

It is important to OSHA's technical staff that they form their own judgments and decisions. A directory of where and what test data were available would be valuable.

A source of information on research in progress which is presently used by OSHA is the Smithsonian Science Information Exchange (SSIE). It is a non-profit service which collects, indexes and disseminates information about research in progress. Project descriptions are supplied primarily by federal agencies as well as by state and local governments, non-profit associations and foundations, universities, and individual investigators. (For further discussion, see Section 4.2.3.) It was suggested that the mechanism employed by SSIE for collection and dissemination be studied for use in a CTSS directory of tests.

2.2.4 Consumer Product Safety Commission (CPSC)

The Consumer Product Safety Commission was established by the Consumer Product Safety Act of 1972. The intent of the Act is to reduce the risk of injury associated with the use of consumer products, either through establishing mandatory safety standards, or by banning products from the market.

CPSC relies heavily on its National Electronic Injury Surveillance System (NEISS), public interest research groups, universities, citizen petitions, and other agencies to identify products that may pose a substantial risk of injury to the public. Priorities are then established for products that require investigation.

The investigation is initiated by analyzing previous tests that may have been conducted on the product or constituent chemical substance. Current sources of information do not provide a suitable mechanism for identifying these tests. TOXLINE, the Smithsonian Science Information Exchange, and personal contacts are the primary information sources used. However, these sources identify only some tests in progress and those in which the results have been recently published. (See Sections 4.2.1 and 4.2.3.)

Older tests and experiments that have not been published may be overlooked. A high priority requirement is a directory of past and present tests conducted by federal agencies, independent laboratories, and industry. The directory should identify the chemical substance under evaluation along with extensive chemical identifiers, objectives of the test, who is conducting the test, and the starting and ending dates of the test.

If the analysis of the previous tests indicates inconclusive results, or no previous tests were available for analysis, CPSC can initiate experiments either through its own laboratory or by an independent contractor. About 200 products per year are tested by CPSC. Its facilities are partially automated, but most data are recorded manually. Since some of the CPSC laboratory procedures are incorporated in the IRLG Testing Guidelines, adherence to these guidelines would pose no problem. In addition to the normal animal toxicity testing guidelines, CPSC is also interested in guidelines for metabolic and bio-availability tests.

CPSC indicated that detailed experimental data which exist only in machine-readable form may present problems in judicial cases involving the defense of a CPSC regulation. Under current rulings, only the hard copy report filled in by the person conducting the experiment may be submitted as evidence in a court.

In order to substantiate a particular regulation, CPSC must thoroughly evaluate test data to determine that there was sufficient information to reasonably support the conclusion that use of the product constitutes a substantial risk. During this risk assessment, the detailed day-to-day test data are examined to determine if the experiment was performed in an acceptable manner and if the data were collected accurately. These procedures are currently done without the assistance of automated facilities. If the test data were in a machine-readable form, and an appropriate on-line analysis capability were available, the time required for this operation and the margin for error would be reduced. Time would also be saved if the test data were presented in a standardized format.

The results of the test data evaluation are part of a "briefing package" which is an overall assessment (health effects, engineering, economics) used to support a regulation. The evaluation may contain graphs, charts, and tables developed from the data analysis. If the test data were in machine-readable form and a generalized software package were available to analyze the data and produce the charts, graphs, and tables, a significant savings in time and effort could be realized.

CPSC is concerned with the confidentiality of testing information. It is CPSC's policy that test data on a product is confidential until a regulation for that product is promulgated. At that time, the information can be released to the public through the Freedom of Information Act. Any Chemical Testing Support System developed should consider this need for confidentiality.

2.2.5 Industrial Trade Associations

Two industrial trade associations which represent the interests of chemical manufacturers were interviewed to determine what impact a Chemical Testing Support System would have on their members. The associations contacted were the Manufacturing Chemists Association and the Synthetic Organic Chemical Manufacturers Association.

Manufacturing Chemists Association (MCA)

MCA has an estimated membership of 200 companies which represents approximately 90% of the chemical industry. One function of the MCA is to administer tests on selected chemicals which are of general concern to one or more of its member companies. At the conclusion of these tests, MCA releases the results to the public. Prior to conducting a test, a survey is made to determine if the chemical substance is currently being tested or has already been tested. TOX-TIPS is an invaluable source for identifying current and past toxicological research projects involving non-proprietary compounds. However, a more comprehensive directory that identifies a larger number of completed tests for both proprietary and non-proprietary compounds is needed. A directory that identified tests on a chemical-specific and generic basis would be useful to avoid redundant testing. (For further information see Section 4.2.4.)

MCA indicated that many toxicologists would find it difficult to accept imposed standardization of data collection since it would tend to reduce innovation in toxicological studies. On the other hand, it would eliminate the provincial views of some agencies and testing facilities through the adoption of a national standard guideline for certain laboratory animal experiments. Standardization would be more acceptable if amendments and improvements could be easily incorporated, and if a certain amount of judgment and interpretation were allowed in conducting the experiment and reporting the results.

Industry would be concerned over any increased costs associated with gathering new data and reporting more information. Their apprehension is based on the increased costs imposed by the reporting requirements of TSCA. Industry is also concerned about the protection of confidential information. A central, shared computer, that collected, stored, and monitored test information while an experiment was being conducted, would not be amenable to industry. Tests are usually conducted confidentially and the results released to the public when the test is completed. If test data were leaked to the public before a test were completed, the premature data might result in conclusions that might be inconsistent with the final results.

MCA indicated that a system that provided for both hard copy and machine-readable data submission would be most desirable. Laboratories would conduct animal studies according to testing guidelines using their own facilities, and submit results and supporting raw data in either hard copy or machine-readable form, depending on the degree of automation. This procedure would provide the best security for confidential data.

Synthetic Organic Chemical Manufacturers Association (SOCMA)

SOCMA is a trade association representing approximately 90 manufacturers of synthetic organic chemicals. Because most of their members are small companies, SOCMA is especially concerned with the problems associated with this group.

SOCMA indicated that adoption of the IRLG Testing Guidelines would impose too much of a burden on small firms to continue testing compounds using laboratory animals. Instead, these firms would use independent laboratories or university laboratories to conduct their tests. SOCMA also indicated that standardization would improve the quality of test data collected in the future.

Member firms would be concerned about the availability of access to chemical testing data. The existence of a directory of tests that have been conducted would prove useful. However, SOCMA is concerned about certain aspects of a directory such as:

- What test results would be included?
- Who would develop the directory?
- How far back would test citations go?
- What sources would be used to obtain information?
- How will included information be evaluated?

SOCMA considers the evaluation of test data and how the evaluation is used to be very important. Once data are cited in literature or information systems, they may be cited in other literature or information systems to support other claims or ideas. This process can continue many times, and in cases where the original test data were never fully evaluated, the results are often misleading or incorrect.

For the most part, the standardization of test protocols and reporting formats was viewed as favorable as long as it was "reasonable." The concern was that the cost of the adoption of standards might outweigh the benefit.

2.2.6 The National Center for Toxicological Research (NCTR)

NCTR represents a joint effort between FDA and EPA to study the long-term, low-dose effects of toxic substances. An extensive research facility now operates with the capacity of maintaining over 80,000 experimental animals. Research activities concerning carcinogenesis, mutagenesis, and teratogenesis, are directed by four primary goals at NCTR[1]:

- determining the adverse effects stemming from long-term, low-level exposure to various chemical substances
- developing experimental data which will facilitate extrapolation of animal studies to humans
- determining the basic biological processes in animals which will improve the validity of extrapolating laboratory results to humans
- developing improved methods and testing protocols for evaluating the relative safety of chemical substances.

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[1] Automated Systems for Research Support Overview, Revision 2, September 1976, p. 1.

A system was needed which would be capable of collecting, storing, and retrieving vast quantities of data generated for each animal under experiment. Unique animal data would include weekly observations, gross and microscopic pathology, blood chemistry, and organ weights. It was estimated that a file on a single animal might require over 3,000 observations. In order to manage this extensive research effort, the Scientific Information Systems Division was assigned the responsibility of designing, developing, and implementing an automated research support system.

A modular, integrated system, the Toxicology Data Management System was subsequently designed to furnish comprehensive, timely, and usable information to aid investigators in conducting research. The system permits the experiment to be monitored and analyzed while it is in progress. This allows a certain degree of flexibility to be judiciously exercised. (For further discussion see Section 4.3.3.)

Interviews with personnel from NCTR yielded the following information:

1. A template fitting on the terminal keyboard provides for a selection among 60-70 observation codes. An additional 250 codes are available on an ad hoc basis.

2. Automated source data entry has decreased the number of errors. The transcription of data from one form (manual) to another (keypunch) affords too much opportunity for miscoding or other kinds of errors.

3. Collection of a wide range of data, from animal breeding to diet preparation to environmental monitoring, is important both as a mangement tool and as an increased measure of experimental control.

4. The present query capability is fairly structured and requires the assistance of an information specialist. NCTR plans to augment the retrieval module with user-prompted, menu selection techniques to permit the direct use of the system by users.

2.2.7 The National Cancer Institute (NCI)

The Divison of Cancer Cause and Prevention of the National Cancer Institute has the responsiblity for conducting research on the etiology and prevention of cancer induced by chemical and physical agents. The Carcinogen Bioassay and Program Resources Branch directs bioassay testing to detect carcinogenic hazards, depending substantially on independent labs as contractors.

In 1968, concern began to grow for the information requirements of the carcinogenic bioassay program, due in part to the increasing amount of data, as well as kinds of data flowing into NCI. Existing personnel could not adequately handle contract administration and evaluation. It was apparent that some mechanism was needed to standardize data collection and data reporting formats to foster analysis and review in a timely fashion with a high assurance of quality.

The Carcinogenesis Bioassay Data System was conceived in order to monitor and evaluate bioassay investigations. This included specifying the kinds of data to be collected and the format in which they were going to be submitted. By computerization at that stage, NCI established a prototype for an automated system for bioassay studies. Over a five-year period, great progress has been made in identifying and standardizing data elements which comprise carcinogenic bioassays.

One of the early considerations was the recognition that a degree of flexibility had to be inherent in the system to allow for scientific developments and the resultant change in data reporting, as well as changes in the state-of-the-art of clinical observations. Initially the Standard Nomenclature of Pathology SNOP coding system was employed, but this method suffered because of the loss of detail and "forced" description of encoding. It was realized that SNOP codes were simply not sufficient for pathology and toxicology, but rather a dynamic language capability was required. Thus, free-text analysis was subsequently added to the system.

NCI has since joined forces with NCTR to provide not only data collection, but maintenance, analysis, and the final reporting of bioassay data. This project is known as the Toxicology Data Management System. Whereas NCTR had developed a highly sophisticated query capability and management information system, NCI provided the expertise in standardized scientific data collection and reporting. (TDMS is discussed in detail in Section 4.3.3.)

NCI stated it would benefit from knowing of the existence of on-going and completed tests as well as having access to the specific test results. For example, the ability to compare test data would be significantly increased, and the awareness of existing test data would assist in assessing further research needs and in augmenting the predictive capability of further testing and experimental design.

2.2.8 Independent Testing Laboratories

Not all chemical manufacturers have their own testing facilities. Instead, tests may be contracted out to independent companies who conduct the experiments. Various government agencies also employ these laboratories for the same purposes. To gain a perspective on the independent laboratory, Sigma Data interviewed Litton Bionetics, one of the largest and most reputable facilities.

Litton is in the process of installing a Hewlett-Packard minicomputer to aid in data collection. A link will be maintained with a mainframe computer where the data is stored. Statistical analysis packages are available to them, such as SPSS, SAS, and BIOMED. Different report-writing formats are available and these are tailored to their individual clients.

In the process of installing an automated system, Litton-Bionetics considered the joint NCI/NCTR Toxicology Data Management System; but due to the hardware and software costs, they opted to develop their own system. However, they reported that they do collect the same data elements as TDMS, only in a different format.

Some data are entered at the source of input, while some records are maintained manually, depending upon the requirements of the client. Data checks are incorporated and these are a direct result of the GLPs. For example, there are flags if an attempt is made to weigh an animal already reported as dead or if a large weight change occurs over a very short time period.

Magnetic tape is permitted for submission of test data to a government agency with two provisions: that it be non-erasable and that it be incapable of being written over. It is not always necessary to submit the laboratory notebook.

Before undertaking an experiment, Litton searches the TOXLINE and MEDLINE databases for the relevant current literature. The former is a primary source for determining the types of toxicity or target organs upon which to focus. LADB (Laboratory Animal Data Bank) provides the normal ranges of various parameters which will be of great value in determining abnormalities. Litton does not report to TOX-TIPS since some of their data are confidential.

Litton, as well as other independent labs, would find a central directory of tests extremely valuable. Furthermore, Litton's present information requirements indicate a strong relationship between LADB and CTSS.

2.3 IRLG Testing Standards and Guidelines Workgroup

The Interagency Regulatory Liaison Group was established to identify, develop, and select general procedures and criteria for various functions that could be uniformly applied to all chemical substances regulated by the participating agencies (EPA, FDA, CPSC, OSHA). Combining and coordinating these functions through cooperative interagency ventures would help in developing ways to reduce the administrative burden and to improve the information exchange process for the regulated industries, the general public, and the participating agencies. The IRLG is divided into the following work groups:

- Testing Standards and Guidelines
- Risk Assessment
- Information Exchange
- Research and Development
- Regulatory Development
- Compliance and Enforcement
- Interagency/Public Communication and Education.

2.3.1 Subject Matter and Scope

The Testing Standards and Guidelines Work Group was established to develop testing guidelines, criteria for interpretations, quality assurance procedures, and other policies relating to the testing of toxic and hazardous substances. Previously this report indicated that three of the four regulatory agencies have developed some form of standards and guidelines for testing chemical substances. It also indicated that there was substantial overlap in the types of chemicals tested and the types of testing methodologies used. These independent activities have resulted in different guidelines and standards.

Each of the agencies has had to assess risks and develop regulations based on information obtained by other agencies or independent organizations. In some cases the materials used for the evaluation was presented in many different formats and judgment had to be exercised because of missing data or improper testing protocol. One of the reasons for creating the Testing Standards and Guidelines Work Group was the scarcity of optimal, scientifically sound toxicological data. As a result, the Work Group will develop guidelines for conducting studies on health and environmental effects that are mutually acceptable and useful to each agency. However, the determination of how to use the information generated by these studies will be left to the individual agency. Every effort will be made by the Work Group to mesh common agency needs and incorporate the results of current agency efforts into the standards and guidelines.

The salient points covered by the Testing Work Group include[1]:

- Criteria for deciding whether a test needs to be done and if so, which tests.

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[1] Report on Progress of the Interagency Regulatory Liaison Group, "New Initiatives," July 1977.

- Guidelines for protocol development for short-term and chronic tests; what constitutes an adequate test?
- Amount and type of data necessary for determining safety; decision scheme for application to a tier system and statistical evalution
- Interpretation of data derived from both short-term tests and chronic tests; are experimental results relevant to a human situation, and what is the significance of pathology observations?
- Quality assurance of laboratory data

2.3.2 Information Requirements

A Chemical Testing Support System would be a mechanism for transforming the information in the testing guidelines into a set of detailed standardized specifications for the collection and reporting of laboratory animal test data. The data collection and reporting formats developed for a CTSS must be in both machine-readable and manual form since some of the laboratories using the guidelines may not have automated procedures.

The structure and data content of the CTSS would be based on the information specified in the guidelines. At the time this report was drafted, the Testing Work Group had draft guidelines for nine types of tests:

- Acute dermal
- Acute inhalation
- Acute ocular
- Subchronic dermal
- Subchronic inhalation
- Subchronic oral
- Teratogenic
- Reproductive

The guidelines were analyzed by Sigma Data to determine broad categories of information that might be common to all types of tests and that would constitute the major subject areas of a CTSS. The categories identified include:

- Experiment identification
- Test substance characteristics
- Animal grouping
- Dosages
- Animal observation
- Facilities
- Gross necropsy
- Microscopic necropsy
- Organ weights
- Hematology
- Blood chemistry
- Litter information
- Animal disease and treatment
- Miscellaneous tests
- Environmental monitoring
- Statistical analysis

Appendix D presents detailed data items by subject category required for the nine types of tests. The information in Appendix D is not intended to represent a complete set of requirements. It was obtained from draft documents that were available at the time this report was written.

2.4 Summarization of User Needs and Objectives

An automated system for CTSS was perceived to be the most desirable and most viable system, based on the following consideration:

- the volume of test data received by each agency is expected to increase with the growth in reporting requirements.
- the standardization of data collection and reporting is conducive to automation.

- the turn-around time from the receipt of test data to the agency decision could be shortened substantially. For example, within FDA where this process has been known to take several years, the time required for product approval could be significantly reduced. Within OTS, short turn-around times are required by law.
- statistical and evaluative analyses employed with test data would be facilitated.

2.4.1 Data Content

In order to integrate the user needs for the CTSS, the following specific requirements were identified by Sigma Data which represents a slight expansion of the system objectives delineated in Section 2.1:

- Test Data Collection
- Test Data Reporting
- Directory of Test Data
- Detailed Analysis of Test Data
- Confidentiality

Test Data Collection: In order for a "system" to be developed, there must be a reasonable and acceptable level of standardization. This facilitates more uniformly controlled experimentation. Since not all users possess automated data collection facilities, provision for both manual and computerized recording mechanisms is required.

Users have stressed that flexibility is essential for reporting pathological observations. While coding schemes would be extremely useful, not all observations necessarily fall into one or another category. It was strongly urged that any developing system recognize the value of unstructured and structured capabilities.

Two problems were delineated which will affect implementation. First, there will be a substantial time lag between when data submission formats are specified and when the requirements are actually followed. Provision must be made for a transition period to avoid requiring that experiments in progress alter their formats for data collection, and thus possibly influencing the results. Secondly, the conversion from hard copy to machine-readable form cannot be easily or accurately accomplished by a keypuncher or even a semi-skilled technician. In many cases, judgments and decisions have to be rendered in the "data transfer" which require expert knowledge in the field. Therefore, retrospective evaluation which would necessitate placing "old" test results into machine-readable form, would be a time-consuming and costly operation. Highly specialized personnel would have to be closely involved in the data interpretation for accurate conversion.

It is desirable to have the capability of monitoring the day-to-day progress of an experiment in order to maximize quality control. A means of analyzing preliminary test results facilitates the identification of certain abnormalities that may necessitate altering the experiment protocol.

Test Data Reporting: As in data collection, there are requirements for standardized reporting formats which must be adapted from the guidelines specified by the IRLG Testing Work Group and the TSCA Sections 4 and 5 testing and reporting rules. The raw data, as well as the summary charts, graphs, and tables must both be available.

Directory of Test Data: Considerable need was expressed for some kind of central directory of all tests which had been conducted as well as those which were in porgress. The existing sources such as TOXLINE, TOX-TIPS, and SSIE, are useful, but each has its limitations. A directory which would include all the tests submitted by industry and those conducted by the government would be extremely valuable. However, the observation was made that all tests are not "equal" and some indications should be given if a test were conducted in nonconformance with the GLPs, for example, or if it were an evaluated or nonevaluated test. A directory must be searchable on a chemical-specific and on a generic basis if the duplication of tests on chemically alike substances is to be minimized. In addition, a separate notation on the kind of test conducted (e.g., acute, subacute, etc.) would further assist in identifying the usefulness and value of completed investigations. Once a determination has been made from the directory that a test is relevant, the location of the raw test data should be indicated. This is primarily useful to the IRLG agencies who are eager to share existing test data for their respective evaluation procedures.

A directory might also provide a means for pinpointing the target areas (e.g., liver, kidney, etc.) susceptible to doses of a particular chemical. Sharing of test results and the information therein is far more efficient than several investigators re-discovering the same result. Industry was most interested in this aspect because it presented no threat to the confidentiality or to the manufacture of their products. Each test should also be accompanied by an abstract of the results.

Detailed Analysis of Test Data: Data submitted in support of test results may be interpreted in various ways. A reviewer/evaluator may consider it useful to analyze raw data in a manner not previously prescribed. By establishing an easily available, analytical capability, evaluators within the regulatory agencies, investigators in industry, and the public would profit immeasurably in terms of time saved and increased confidence in statistical results.

If the studies were conducted and submitted in a standard format, the CTSS could be used to conduct rapid evaluations (risk assessments) in a somewhat consistent manner. This would decrease the number of tests that were rejected due to inadequate data. If the test data reveal that insufficient data have been submitted, additional tests may be required to obtain meaningful results before any determinations are made regarding its carcinogenicity, for example.

Confidentiality: Industry is particularly sensitive to the concept of shared databases and the vulnerability inherent in the competitive market-place. Independent laboratories must also be responsive to their customers, some of which are private firms. A means of establishing a secure database, at least through the premarket notification stage, is absolutely essential. It is conceivable that some test data will never be public and the design of any system must take this into account.

Table 2-1 categorizes the information gathered from the interviews to allow user requirements to be perceived relative to one another. The IRLG is not a user per se. However, since they have addressed the issue of standardized data collecting and reporting, it was considered pertinent to include them. An "X" appears in the appropriate box if the user indicated a preference for a particular requirement. If the user was ambivalent or did not express a need, the space was left blank.

2.4.2 Data Access

Based upon the requirements specified above for Data Collection, Data Monitoring, and Data Reporting, certain considerations follow in terms of the requirements of a retrieval system:

- to support standardized data collection, manual and automated recording mechanisms are needed
- to support the flexibility needed for recording observations, a free-text searchable field might be a solution
- to support the regular monitoring of experiments in progress, a rapid processing or turnaround time for the recorded data is needed

Table 2-1

Summary of User Requirements

	EPA	FDA	CPSC	OSHA	INDUSTRY	INDEPENDENT LAB	GOVERNMENT LAB	IRLG
Test Data Collection								
Standardization	X	X	X	X	X	X	X	X
Monitoring	X						X	
Hard Copy		X			X	X		
Machine-readable format	X	X			X	X	X	
Test Data Reporting								
Standardization (raw & summary data)	X	X	X	X	X	X	X	X
Hard Copy					X	X		
Machine-readable format	X		X		X	X	X	
Test Directory	X	X	X	X	X	X		
Confidentiality	X	X	X		X	X		
Test Data Evaluation								
Large Volume	X	X					X	
Significant Turnaround Time	X							
Comparative Analysis	X	X	X		X		X	

- to support Federal access to the system and private access to the analytical software and to non-proprietary test data, several implementation options must be considered

A Chemical Testing Support System would combine and consolidate the information specified in the various guidelines into a generalized system that would be responsive to the needs of each type of test. The design of the CTSS should be open-ended in order to accommodate change and a phased implementation. The specifications of guidelines will change over time as new testing methods and approaches are developed and approved. These will have to be easily incorporated into the CTSS. Since guidelines for some types of tests have not been developed yet, the CTSS must support an incremental implementation strategy.

If industry is requested to submit data in a designated format to a government agency, two immediate problems can be identified: a dictionary conversion and a file conversion. A standardized dictionary of observation and clinical codes is one of the most difficult projects to develop yet is highly desirable. Some systems employ a narrative text for observations for manual or computerized storage. Standardized terms, or mapped vocabularies, are needed for clinical observations, gross and microscopic pathology, and teratology. A file conversion program for test data to conform to government requirements is also possible as long as the data collected are clearly specified and the specifications for conversion are given.

With regard to Data Analysis, several other access considerations are consequential to the requirements of data content. The detailed analysis portion of the CTSS could be used to assist in the evaluation of other tests, and to prepare the supporting graphs, charts, tables, statistics, etc., in an on-line mode, faster than current procedures. The necessary software to create the graphic displays as well as to provide statistical analysis must be incorporated into the system. In order for toxicologists and other laboratory investigators to conduct their own analyses, user-prompting should be built into the system.

Standardization of data collection and reporting will greatly facilitate the evaluation of test results. The use of a computer to conduct the statistical analysis is easily accomplished.

Since some private laboratories have already developed their own statistical analysis capability, the analysis program component of a CTSS was not considered to be particularly valuable to them. On the other hand, those industrial laboratories which do not have an analytical capability, particularly the smaller labs, would find this capability extremely valuable.

There may be problems stemming from the storage (temporary or permanent) and evaluation of confidential data on a large, shared computer facility. Substantial precautions would be necessary to ensure the security of test data supplied by industry. For example, a complex user identification coding process could restrict access to certain portions of the data base. (An extensive discussion of this issue appears in a previous report prepared by Sigma Data entitled, "A Study of System Requirements for Implementing a Chemical Substances Information Network.")

Lastly, there will be several operational requirements with respect to input and output for both the Directory of Tests file and the Analytical file. The Directory must support input from many sources and as the index guide to the CTSS, easy and direct access must be assured. The Analytical File will also have input from many sources (government and industrial laboratories); however, this input or data submission should be in a standardized format. IRLG agencies will require direct access to the file for both proprietary and nonproprietary data; whereas the private sector should be permitted limited access in order to protect proprietary data. There has been an assumption made by the staff at OTS that by permitting the private sector to the analytical capability of CTSS, there would be an added incentive to industry to collect and submit test data in the required format.

3.0 PROPOSED SYSTEM

3.1 General System Description

Based on the informational needs expressed by users, Sigma Data recommends the development of an integrated, modular system consisting of both nonautomated and automated procedures. The total system would be supported by a number of functional subsystems which include:

- Data Collection
- Data Submission
- Storage and Conversion
- General Inquiry
- Detailed Analysis and Evaluation

Figure 3-1 illustrates the interrelationships among the five subsystems of the proposed CTSS. Information generated by a particular subsystem will be utilized by other subsystems, but the design of the system will enable the various functional subsystems to operate independently of each other. This design approach is based on the broad spectrum of users (industrial, research, federal government, public interest groups) that are expected to participate in the CTSS, and on the diverse informational needs of these various users. An integral part of the CTSS design concept is the ability to implement the subsystems independently. This design philosophy permits users to develop, incorporate, or utilize any number of functional subsystems, depending on their individual requirements.

The Data Collection subsystem will be concerned with testing protocols and the gathering of detailed test data on health effects studies involving laboratory animals. The studies will be conducted according to the standards and guidelines for various types of tests such as those developed by the Testing Standards and Guidelines Workgroup of the Interagency Regulatory Liaison Group, regulations of individual agencies, and the Good Laboratory Practices (GLP). The standardization explicit in the IRLG-GLP guidelines will be mandatory at the Data Submission level, but flexible at the Data Collection level. Thus, what data are to be collected and the format in which they are to be reported will be stipulated, but how the data are actually recorded at the time of collection remains unrestricted.

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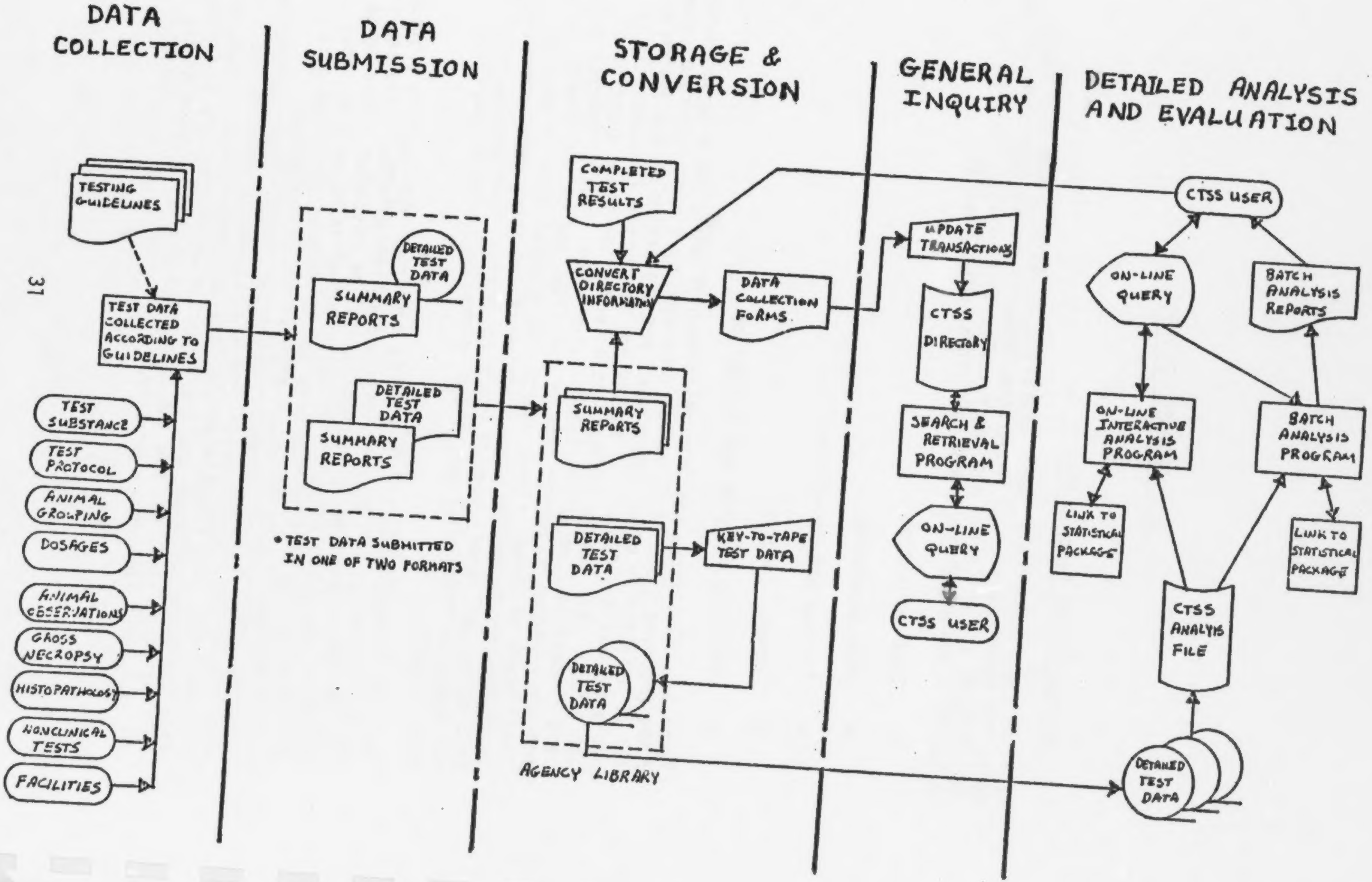
FIGURE 3-1

CTSS FUNCTIONAL INTERFACE DIAGRAM


DATA COLLECTION
DATA SUBMISSION
STORAGE & CONVERSION
GENERAL INQUIRY
DETAILED ANALYSIS AND EVALUATION
TESTING GUIDELINES
TEST DATA COLLECTED ACCORDING TO GUIDELINES
TEST SUBSTANCE
TEST PROTOCOL
ANIMAL GROUPING
DOSAGES
ANIMAL OBSERVATIONS
GROSS NECROPSY
HISTOPATHOLOGY
NONCLINICAL TESTS
FACILITIES
DETAILED TEST DATA
SUMMARY REPORTS
DETAILED TEST DATA
SUMMARY REPORTS
* TEST DATA SUBMITTED IN ONE OF TWO FORMATS
COMPLETED TEST RESULTS
CONVERT DIRECTORY INFORMATION
DATA COLLECTION FORMS
SUMMARY REPORTS
DETAILED TEST DATA
KEY-TO-TAPE TEST DATA
DETAILED TEST DATA
AGENCY LIBRARY
UPDATE TRANSACTIONS
CTSS DIRECTORY
SEARCH & RETRIEVAL PROGRAM
ON-LINE QUERY
CTSS USER
CTSS USER
ON-LINE QUERY
BATCH ANALYSIS REPORTS
ON-LINE INTERACTIVE ANALYSIS PROGRAM
BATCH ANALYSIS PROGRAM
LINK TO STATISTICAL PACKAGE
LINK TO STATISTICAL PACKAGE
CTSS ANALYSIS FILE
DETAILED TEST DATA

The Data Submission subsystem will assemble the information concerning an animal study into an appropriate "package" for submission to one of the federal regulatory agencies. The "package" will include detailed test data collected by the laboratory during the course of the experiment and various summary reports derived from the detailed data. The detailed test data and summary reports will be submitted in a standard format that meets the specifications outlined in the IRLG Testing Guidelines and the GLPs. This standardization will enable regulatory agencies to review and evaluate animal studies in a consistent manner, and will promote the sharing of test data among federal agencies, industry, and academia.

The Storage and Conversion subsystem will include the archives of animal study data and the conversion of this information into a format that can be used to update the CTSS Directory and the CTSS Analysis File. Because of legislative and confidentiality requirements, test laboratories will submit animal study information directly to the appropriate regulatory agency. Each agency will have control over its library of test results and will disseminate the information according to its regulations. In this way, individual agency confidentiality restrictions will be preserved.

The General Inquiry subsystem will provide a "current awareness" capability on animal studies that have been completed or are currently being conducted. Users would be able to receive answers to such questions as:

- What tests have been conducted for a particular chemical?
- Who conducted the test?
- When did the test start?
- When will the test be completed?
- What type of test was conducted (acute, chronic)?
- Where is the detailed test data located?

The General Inquiry subsystem will permit regulatory agency managers to determine if a similar test has been completed or is currently in progress before requiring an animal study to test for a particular chemical substance. Duplicate efforts among agencies and research organizations would be avoided. Evaluation teams in regulatory agencies or laboratories could also use the subsystem to locate other tests that might be used for comparison when conducting a risk assessment.

The Detailed Analysis and Evaluation subsystem will provide an ability to establish, maintain and provide access to a CTSS Analysis File. The Analysis File will provide the capability of examining and investigating detailed test data on animal studies that were conducted according to IRLG-GLP Testing Guidelines, and were submitted in the standardized format. The Detailed Analysis and Evaluation subsystem will fulfill the requirement of researchers and analysts in government and industry to conduct independent evaluations of animal studies. While standardized summary reports are useful, they are often insufficient. The detailed test data must be reviewed to determine if certain protocols were followed or to derive additional information or analyses not presented in the summary reports.

The remainder of this section discusses the subsystems of the Chemical Testing Support System in more detail.

3.2 Data Collection Subsystem

The Data Collection subsystem represents the initial step in establishing a viable standardized source of information on animal studies. The data collected at this stage of the Chemical Testing Support System will provide a foundation upon which future reviews, evaluations, judgments, and analyses will be based. Therefore, the data necessary for such a function must be complete and accurate.

"Complete" data required to support an experiment associated with the CTSS includes both scientific data elements and managerial or control data elements. Scientific data include such information as the type of tumor found and the number of animals dying at a particular dose level. These data are used to make inferences about an experiment. Managerial or control data, on the other hand, include the time an observation was made, and the name of the person conducting a gross necropsy. Although this information does not have direct scientific value, it is important as a verification of the adherence to the test protocols. Data collected "accurately" implies that no transcription errors or incorrect observations were recorded in the data collection process. Data errors lead to faulty statistics which can adversely affect experimental results and conclusions.

The importance of data collection has been emphasized by recent incidents in which animal studies have been cancelled or invalidated due to inconsistent data reporting, improper animal care, and poorly conceived protocols. These situations have been caused by the absence of standards for conducting animal studies. In order to ensure the quality and integrity of test data collected for the CTSS, it is proposed that participating laboratories conduct experiments according to the Good Laboratory Practices developed by the Food and Drug Administration.

FDA proposed the GLPs as a result of finding inconsistent data during the review of nonclinical studies submitted to the agency. Some of the problems detected by FDA and published in the Federal Register include[1]:

- Poorly conceived experiments
- Inaccurate analysis of test data
- Improper supervision of personnel
- Improperly trained personnel
- Failure to verify accuracy and completeness of scientific data
- Failure to adhere to defined protocol
- Inaccurate observations and administration of test substance
- Inaccurate recordkeeping

The GLPs are mainly concerned with control information and do not specify what organs are to be examined during necropsy, what information is to be collected in a blood test, nor what tabulations and graphs are required for a particular type of test. However, these types of information are necessary for a complete and in-depth review and analysis of an animal study. In order to satisfy these requirements, the Testing Standards and Guidelines developed by the Interagency Regulatory Liaison Group must be adhered to by the Data Collection subsystem. (See Section 2.3.) The Data Collection subsystem, therefore, provides the mechanism for gathering the necessary data to support the animal study submission requirements of the regulatory agencies. The various formats for data submission are discussed in Section 3.3.

The potential users of the Data Collection subsystem will include those industrial, independent, governmental, and research laboratories that conduct studies for the various regulatory agencies. The data collection mechanisms in these laboratories include full automation, semi-automation, and manual procedures. Many of these laboratories have developed sophisticated data collection systems requiring lengthy implementation periods and large developmental costs. For this reason, under the proposed CTSS, laboratories would be able to use their present mode of data collection instead of adopting a standardized data collection facility. Also, since some laboratories perform work for other clients in addition to the regulatory agencies, IRLG standardization could create conflicting requirements. Modifying systems to meet IRLG-GLP guidelines that are being developed in an environment of constant review and change would impose an unnecessary expense on laboratories.

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[1] 41 FR 51207.

Each laboratory would have to ensure that its system collected the required information specified in the IRLG-GLP guidelines. The CTSS Data Collections subsystem, therefore, identifies what data are to be collected, but does not specify how the data are to be collected.

Monitoring of tests in progress poses several problems, particularly with respect to confidentiality. Essentially, monitoring of tests is the concern of individual laboratories since it is, in many respects, a validation of test procedures. However, monitoring can be easily employed by government laboratories using minicomputers for data collection as has been developed by NCTR and NCI. In any case, once standardization of data collection and reporting are implemented in a machine-readable format, monitoring can be easily incorporated into an existing automated system.

3.3 Data Submission Subsystem

The Data Submission subsystem of the CTSS will assemble and format the data obtained by the Data Collection subsystem into a "package" that would be submitted to one of the regulatory agencies in the form of a final report. The production of this "package" is the repsonsiblity of each testing laboratory. The final report on an experiment will include information in a predefined standard format consisting of:

- Detailed or "raw" data
- Summary reports derived from the detailed data

The CTSS will accept detailed data submitted in either hard copy or machine-readable form. The detailed test data must be "complete" in that they must include all the experimental and control information required to reconstruct the entire experiment at a later time by the Detailed Analysis and Evaluation subsystem. This will permit independent review of an experiment by government agencies, industry, and other concerned groups.

Although the detailed data and summary reports will be in a standard format, they must be designed so that they can easily accommodate change and expansion. The IRLG Testing Work Group will be developing new guidelines for various types of tests, as well as modifying existing guidelines. For this reason, the records must be organized using flexible, general formats so that modifications and additions can be incorporated into the Data Submission subsystem with a minimum amount of effort and disruption to the existing system.

The remainder of this section discusses the three types of documents included in the Data Submission subsystem.

3.3.1 Hard Copy Detailed Test Data

The detailed data submitted in hard copy will consist of a series of preformatted worksheets. The animal study information will be divided into logical groupings of data that relate to similar functions. Since a modification of hard copy worksheets can be difficult, a functional data division adds a measure of flexibility when data submission expansion is required. As new functions are defined, additional worksheets can be developed. These hard copy worksheets could be used as the data collection mechanism for laboratories conducting experiments in manual or batch mode, and as a back-up procedure for automated data collection systems.

Since the Data Submission subsystem specified a standard format for test data and reports and since some laboratories already have their own automated data collection system, information must be converted from one form to another. Conversion is not a problem for straight forward data elements such as species, strain, CAS registry number, sample number, preparation number, food supplier, laboratory name, and group number since this information can be directly transferred to the standard format. However, data elements such as mode of storage, sex, type of bedding materials, route of administration, and cage contruction which may be referred to in different terminology must be transformed into a standard format using a series of conversion tables. Data elements that may use different units of measure such as animal weight, age (days, weeks), amount of preparation, food consumption, date of observation (Julian, MMDDYY, YYMMDD), or concentration can be converted into data elements with a standard unit of measure using transformation algorithms.

A significant problem, however, exists in converting the data associated with animal observations such as gross necropsy and histological examination data. A number of coding schemes for this type of information exists. Some laboratories employ codes suited to particular types of tests they conduct, while others rely on free-text narratives. If the CTSS is to make effective use of observation, gross necropsy, and histological data, the information must be recorded in a manner conducive to automated search and retrieval systems, must include data for all types of tests, and must be able to note unusual or unforeseen situations. (A more detailed explanation of observation, gross necropsy and histological data is given in Section 3.3.3). Since this type of information is extensively used to determine test conclusions, errors introduced into the system at this stage of the experiment could jeopardize the validity of an entire experiment. For these reasons, laboratories should make every attempt to adopt standards for recording observations and gross necropsy and histological data into their data collection systems, but they should also be cognizant of the absolute necessity for flexibility. An option of "individualized" observations will be more acceptable to toxicologists.

Each worksheet would identify the function being recorded and each data element associated with the particular function. Space will be provided next to each data element for entering the value, code, or description associated with the particular data element. Since the worksheets or documents will be used in the Storage and Conversion subsystem of CTSS (Section 3.4) to transform the hard copy information into a machine-readable format for the CTSS Analysis File, the worksheets will be designed to incorporate aids for keying procedures. These aids will enable the worksheet data to be keyed directly into transactions that have the same format as the machine-readable detailed test data (section 3.3.2). These aids will be preprinted on the worksheet and will include identifiers for the type of transaction, the individual data elements, the prescribed length of the value, code, or description of each data element.

Appendix A illustrates the information to be included in detailed test data worksheets. Control or management information was derived mainly from the GLPs (Section 3e.185) while experimental data elements were derived from the IRLG Testing Guidelines presented in Appendix D. Sigma Data divided the detailed test data required by the CTSS into 23 functional categories, each represented by a worksheet, which include:

01 - Experiment Identification - Indicates the laboratory conducting the test, start and end dates, type of experiment responsible personnel, chemical being tested, and the objectives of the experiment.

02 - Summary and Conclusions - A summary of the data collected, an analysis of the data, and a statement of the conclusion drawn from the analysis.

03 - Test Substance Batch Data - Describes physical and chemical characteristics of each test substance batch used for preparations. The Batch Number provides a link to the test substance preparation.

04 - Test Substance Preparation Data - Describes the physical and chemical characteristics of various test substance preparations used in dosing animals. The Preparation Number provides a link to dose regimens.

05 - Colony Data - Identifies the animals used in the experiment and in what groups they were placed.

06 - Animal Group Data - Identifies the various characteristics of each test group in the experiment and identifies each animal within the group.

07 - Dose Regimen - Indicates the characteristics of the various doses administered to a particular group.

08 - Laboratory Personnel Data - Lists appropriate personnel involved in conducting the experiment. This provides a mechanism for identifying persons conducting observations, gross necropsy, histological examinations, etc.

09 - Individual Animal Observation - Indicates the results of a particular animal observation including the time and person conducting the observation. Recording clinical signs poses significant problems. The variety and number of clinical signs required by the IRLG for animal observation indicates that a comprehensive recording scheme will have to be used. The scheme would consist of two levels of recording clinical signs, coded and free-text. The coding scheme would identify both physical and behavioral characteristics covering a wide number of categories. Because all possibilities cannot be anticipated, and because accurate clinical observations are vital, the worksheet will provide for recording judgmental or individual observations jn a natural language (that is, non-coded) format.

10 - Individual Animal Gross Necropsy - Indicates the results of a gross necropsy including the time, organs examined and the person conducting the examination. Recording gross necropsy results poses the same problems encountered in Animal Observation. Therefore, a similar two-level recording scheme (codes and free-text) will also be employed for gross necropsy results.

11 - Individual Animal Histopathological Examination - Indicates the results of a histopathological examination including the time of observation, the tissues examined, and the person conducting the examination. Recording histological findings poses the same problems encountered in Animal Observation. Therefore, a similar two-level recording scheme (codes and free-text) will be employed for histopathological results.

12 - Organ Weights - Indicates the weights of various organs for a particular animal.

13 - Hematology Analysis - Presents the results of a hematology test for a particular animal.

14 - Blood Chemistry Analysis - Presents the results of a blood chemistry test for a particular animal.

15 - Residue Analysis - Presents the results of a residue analysis test for a particular animal.

16 - Cholinesterase Analysis - Indicates the findings associated with a cholinesterase test for a particular animal.

17 - Urinalysis Results - Indicates the findings of a urinalysis for a particular animal.

18 - Individual Animal Disease and Treatment - For each animal, identifies any disease contracted during the experiment, indicates any treatment that was administered, and explains the final outcome of the disease.

19 - Environmental Monitoring - Indicates the exposure to light, temperature, and humidity for a group or range of groups. Also indicates the actual temperature and humidity at specified times during the experiment.

20 - Animal Feed Data - Indicates the type of feed and how it is given to a group or a range of groups.

21 - Animal Bedding Data - Indicates the type of bedding used in the experiment.

22 - Animal Cage Data - Indicates the type of cage and caging conditions for a group or a range of groups.

23 - Equipment Maintenance - Records instances of equipment maintenance. Indicates the results of inspection or calibration, when they were conducted, and who performed the maintenance.

3.3.2 Machine-Readable Detailed Test Data

Because the data submission package must be uniform whether submitted in hard copy or machine-readable form, potential transactions or sets of data on magnetic tape should correspond to the 23 hard copy worksheets defined in Section 3.3.1. Although there are many schemes for organizing data into machine-readable form, not all of them could easily accommodate changes or additions to the data submission package which are important to a CTSS.

In order to provide the maximum flexibility, each transaction should be of variable length with a predefined format that would be organized in a general manner. Each transaction would consist of a transaction identifier followed by a series of data element identifiers and the information associated with the data element. Each machine-readable transaction would be defined by a specification table which would consist of the transaction identifier, data element identifiers, data element descriptions, and data element value lengths.

To illustrate how a machine-readable transaction might be defined in the CTSS, Worksheet 11 - Individual Animal Histopathological Examination is used as an example. Table 3-1 presents the format of the transaction specification table for Worksheet 11. Figure 3-2 illustrates the coding of a typical transaction. The transaction code appears in the first two positions of the transaction record. Following the transaction code are a variable number of sets of data element identifiers and associated data values. The data element identifier and length of data value are determined from the transaction specification table. Since the identifier length and data length are predetermined, a software program could easily scan the transaction and process various data elements. Data Element Identifier 99 indicates the end of the transaction.

Worksheet 11 indicates that the findings for a number of organs can be recorded. This implies that Data Element Identifiers 06 through 10 can appear more than once; i.e., they are a repeating group. This situation poses no problem in the expanded transaction and is illustrated in Figure 3-2. If data elements within a repeating group have no associated values, they need not be recorded in the transaction. This is illustrated in the second occurrance of Data Element Identifier 06 in Figure 3-2. The organ examined and coded findings are recorded but Data Element Identifiers 08, 09, and 10 are not recorded. This data organization scheme provides a great deal of flexibility. If, at a later time, new data elements are specified for a particular function, the only requirement will be to add a new Data Element Identifier and Data Element Length to the specification table. Transactions constructed prior to the addition are not affected. Space will be saved by requiring only data elements that have associated values to be recorded.

TABLE 3-1

MACHINE-READABLE TRANSACTION SPECIFICATION TABLE

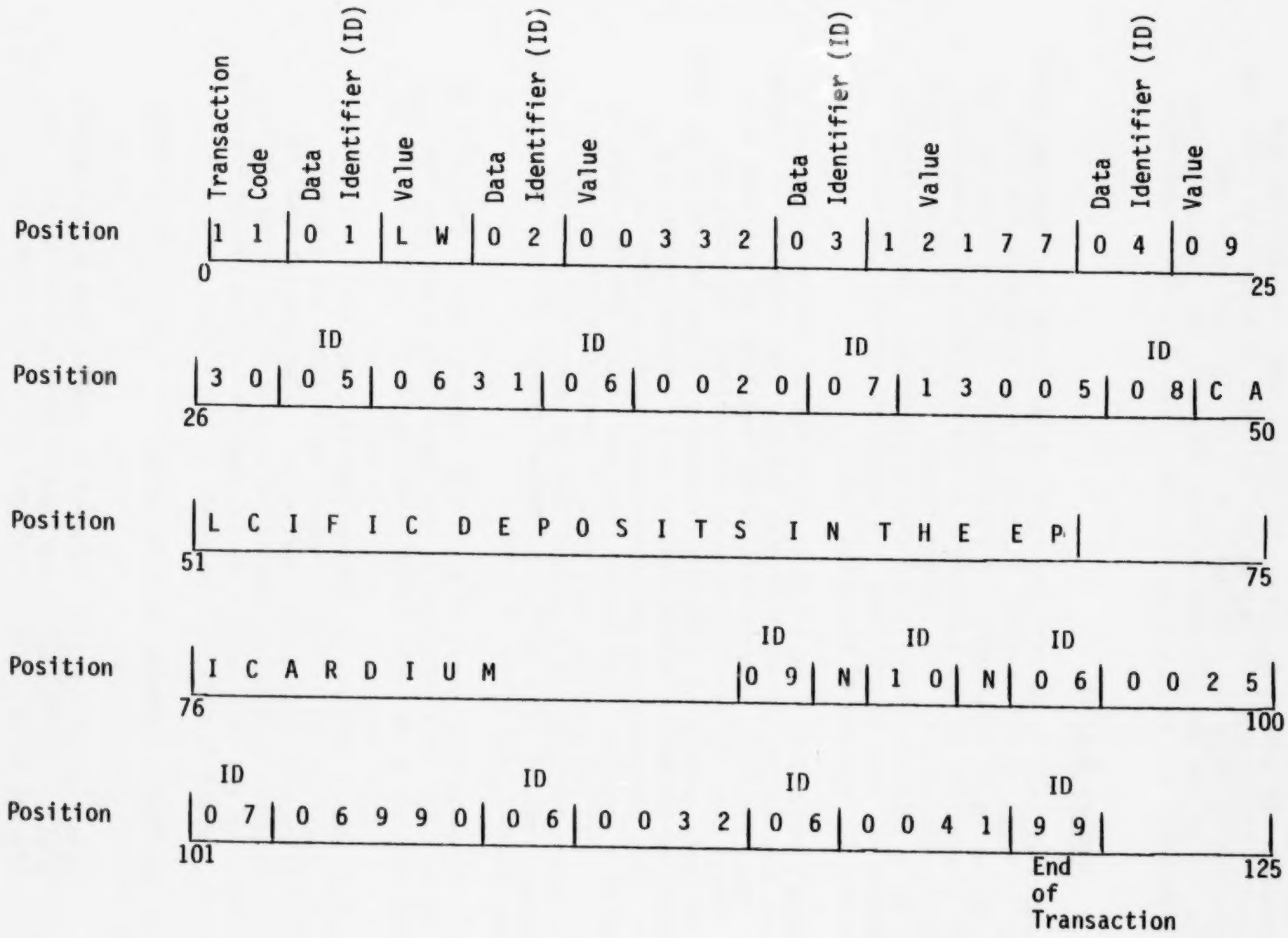
Transaction: Individual Animal Histopathological Examination

Transaction Code: 11

Data Element Identifier	Data Element Length	Data Element Description
01	2	Group identification code
02	5	Animal identification code
03	6	Date conducted (MMDDYY)
04	4	Time conducted (HHMM)
05	4	Person conducting examination
06	4	Organ examined (code)
07	5	Coded findings
08	40	Free-text description of findings
09	1	Caused death (Y,N)
10	1	Caused moribundity (Y,N)
99	0	End of transaction

FIGURE 3-2

EXPANDED MACHINE-READABLE TRANSACTION


Transaction Code
Data Identifier (ID)
Value
Data Identifier (ID)
Value
Data Identifier (ID)
Value
Data Identifier (ID)
Value
Position
1 1 | 0 1 | L W | 0 2 | 0 0 3 3 2 | 0 3 | 1 2 1 7 7 | 0 4 | 0 9
0
25
ID
ID
ID
ID
Position
3 0 | 0 5 | 0 6 3 1 | 0 6 | 0 0 2 0 | 0 7 | 1 3 0 0 5 | 0 8 | C A
26
50
Position
L C I F I C D E P O S I T S I N T H E E P
51
75
ID
ID
ID
Position
I C A R D I U M | 0 9 | N | 1 0 | N | 0 6 | 0 0 2 5
76
100
ID
ID
ID
ID
Position
0 7 | 0 6 9 9 0 | 0 6 | 0 0 3 2 | 0 6 | 0 0 4 1 | 9 9
101
125
End of Transaction

Construction of the machine-readable test data would be up to the individual testing laboratory. A magnetic tape medium is proposed because it represents the most common means of storing and transporting data. The tape specifications will depend on, and must be compatible with, the computer used to store the CTSS Analysis File (Section 3.6). For instance, if an IBM 360/370 machine were utilized, the tape specifications might call for an unlabeled, 9-track, 1600 BPI, ASCII code tape.

3.3.3 Summary Reports

The summary reports to be included in the data submission "package" will consist of those tables, graphs, and charts that summarize the data collected during an experiment. The information in these reports will provide an overview of the experiment to aid analysts and researchers in drawing conclusions. The summary reports will not provide the capability for a detailed analysis and evaluation because certain control information will not be provided. In addition, certain tables and graphs will be reported at the group level.

The summary reports will be a set of preformatted documents similar to the hard copy worksheets which display appropriate groupings of information. Data for these reports will be derived from the detailed test data. Since many testing laboratories will collect and store the detailed tests data using automated procedures, Sigma Data proposes that the reporting documents be preformatted on a "computer compatible" medium. This would include continuous-form documents that could be printed by a computer. The header, row, and column spacing would be compatible with the spacing required by a computer printer. In this way, software packages could be developed to generate automatically the summary reports, thus avoiding a manual transcription procedure that is time consuming and prone to error.

Appendix B presents a number of prototype summary reports that will be required by CTSS. The information for these reports was obtained from the IRLG Testing Guidelines (Appendix D) and the GLPs (Section 3e.185).

The report models reflect the information that was available in the draft documents at the time this report was written and are not intended to represent an all-inclusive set. They are intended to be guidelines for developing reports to be used in the actual implementation. As the IRLG Testing Guidelines are refined and/or expanded, additional report formats will be added to the list.

Each of the report formats shown in Appendix B is discussed in more detail below:

> Animal Group Profile - Identifies the various groups within a study and identifies each animal within a group. Average animal weights and ages are also provided.

Dose Levels by Test Group - For different dosage levels administered to a group, indicates the amount, how and when they were administered, and the average age of the animals at the first dosage.

Weight Change and Food Consumption by Individual Animal - In graph form shows the body weight and food consumption at specified time intervals for each animal.

Average Weight Change and Food Consumption by Group - In graph form shows the average body weight and average food consumption at specified time intervals for each group.

Physical/Behavioral Observations by Individual Animal - By animal, indicates when an observation was made and a description of appropriate physical and behavioral signs that were observed.

Summary of Clinical Observations by Test Group - By test group, indicates each type of clinical sign that was observed, how many animals showed the sign, when it first appeared, and the average age of animals that died and showed the sign.

Incidence of Physical/Behavioral Observations by Test Group - For each clinical sign observed during the study, indicates the number of animals in each group showing the sign.

Gross Necropsy Examination for an Individual Animal - For each animal necropsied, indicates what organs were examined and any abnormalities that were observed.

Summary of Gross Necropsy Examination by Test Group - For each abnormality observed during all necropsies in a study, indicates the number of animals in each group out of the total number of animals that showed the abnormality.

Histological Examination for an Individual Animal - For each animal examined, indicates what tissues were examined, a description of any abnormalities, the number of lesions or tumors, and whether the tissue caused death or moribundity.

Summary of Histological Examination by Test Group - For each abnormality observed during all histological examinations in a study, indicates the number of animals in each group out of the total number of animals that showed the abnormality.

Counts of Tumors and Lesions by Individual Animal by Test Group - For each animal within a test group, indicates the number of non-neoplastic and pre-neoplastic lesions, and the number of benign and malignant tumors.

Counts of Tumors and Lesions by Test Group - For each test group, indicates the number of animals of the total number of animals examined that showed signs of non-neoplastic and pre-neoplastic lesions, and benign and malignant tumors.

Number of Occurrences of Each Type of Tumor - For each type of tumor or lesion observed in the study, indicates the number of occurrences of that tumor or lesion for each test group.

Deaths of Animals with Tumors or Lesions by Time Interval by Test Group - In graph form for each test group, indicates by time interval the number of animals that died, showed tumors or lesions, died because of a tumor or lesion, and were moribund because of a tumor or lesion.

Count of Tumors or Lesions in Dead Animals by Test Group by Time Interval - For each time interval, indicates each type of tumor or lesion found in dead animals and the number of each type of tumor or lesion found in each test group.

Organ Weights by Individual Animal - For each animal, indicates the body and brain weight, and the ratio of various organ weights to body and brain weight.

Average Organ Weights by Test Group - For each test group, indicates the average body weight of all animals in the group, and the average weight and organ/body ratio of various animal organs.

Dose Response Curve - In graphic form, indicates the percentage of animals showing a positive response for the various dose levels within an experiment.

Testing and Evaluation Results by Individual Animal - For each animal within a group, indicates what nonclinical test was conducted, when it was conducted, and the results of the test.

Infectious Diseases and Treatment by Individual Animal - For each animal within a group, indicates any disease contracted, time it was observed, any treatment administered and the eventual outcome of the disease.

Number of Animals Alive and Dying for Each Time Interval by Test Group - In graph form, shows the number of animals alive and the number of animals dying in a particular time interval.

Number of Animals Exposed and Dying by Group - For each group, indicates the number of animals in the group, the number showing signs of toxicity, the number that died, and the average time of death after dosing.

Survival and Death by Time Interval by Test Group - For each time interval, indicates the animals remaining alive, the number that died, the number dying other than by sacrifice, and the number sacrificed and the number moribund at the time of sacrifice.

Age at Death and Time of Death by Individual Animal - For each animal within each group, indicates the age at the start of the test and at death, time the animal died, whether it was sacrificed or moribund, and the time of necropsy if it was necropsied.

Animals Not Subject to Necropsy - For each animal within each group that was not necropsied, indicates the reason necropsy was not performed.

Maternal Data by Individual Animal by Test Group - For each pregnant female within a group, indicates the age at start of test, date of pregnancy and delivery, various organ weights, and abnormal delivery signs.

Pregnancy Data by Test Group - For each group, indicates the number of animals in the group, number dying, number pregnant, and the average maternal body weight change.

Fetal Data by Litter by Test Group - For each litter within a group, indicates the number of live and dead fetuses, live fetal weight, sex, implantations, and various abnormalities.

Anomaly Data by Litter by Test Group - For each litter within a group, indicates the number examined by necropsy, fetuses found having anomalies, the number examined for skeletal anomalies, and the number of fetuses found having skeletal anomalies.

Litter and Abnormality Data by Test Group - For each group, indicates the length of gestation, number of reproductive abnormalities, number of live and dead offspring, and any nesting and nursing abnormalities.

Litter and Fetal Examination by Test Group - For each test group, indicates the number of litters examined, number of implantations and live fetuses, live fetal weight, the number of fetuses and litters bearing anomalies, and the number of abnormal fetuses per litter.

Temperature Measurement by Time - In graphic form, indicates the temperature at specified time intervals to which a group is exposed.

Humidity Measurement by Time - In graphic form, indicates the humidity at specified time intervals to which a group is exposed.

Concentration of Test Substance at the Breathing Zone by Time - In graphic form, indicates the concentration of the test substance at the breathing zone at time intervals.

The IRLG Testing Guidelines also will require additional information in the summary reports such as that related to the identification of an experiment in hard copy form. This information is not in graphic or tabular form, and is not included in Appendix B. Since several of the hard copy worksheets (Appendix A) supply the required information, they could be included in the summary reports portion of the data submission package. For instance, worksheets 01 and 02 record appropriate experiment identification, summary, and conclusion information.

3.4 Storage and Conversion Subsystem

The Storage and Conversion subsystem will provide the capability to store or archive the data submission "packages" received by the federal regulatory agencies, and will convert the information into a form that could be used to update two data bases in the Chemical Testing Support System: The CTSS Directory and the CTSS Analysis File. These two data bases are described in more detail in Sections 3.5 and 3.6.

The confidentiality requirements of some Federal agencies, such as FDA and CPSC, require strict control over any submitted test data. In these cases, each agency will be responsible for establishing and regulating its own library of animal test data. Each library will consist of summary reports and the detailed test data in either hard copy or machine-readable form. As the confidential status on test data is lifted, the agency could disseminate the information to other agencies and the general public. Agencies or research organizations that are not bound by confidentiality requirements could combine efforts to establish and maintain common test data libraries.

The remainder of this section discusses the conversion of information to support the two CTSS data bases.

3.4.1 CTSS Directory

The value in maintaining a directory of test data will be contingent upon the active role of regulatory agencies and other organizations in routinely supplying input. Input forms must be available to record the required data to update the CTSS Directory. The input forms will provide for the complete identification of animal studies. Several events should trigger the submission of information to the CTSS Directory:

- The requirement by a regulatory agency that a test be conducted
- The submission of test data in support of product registration
- The independent evaluation of tests

Industry could be relieved from submitting data concerning tests in progress when those tests were of proprietary value. When tests are submitted in support of product registration however, certain test identification, description, and summary result information will be entered in the Directory. If the test was conducted according to the IRLG-GLP guidelines, Worksheets 01 and 02 (Appendix A) could be used to provide the required information.

Incorporating already completed studies into the Directory will require some measure of selection due to the sheer volume of material as well as to existing awareness services (TOX-TIPS, TOXLINE). However, under Section 8 (d) of TSCA, lists of studies conducted pertaining to a chemical in commerce or proposed for commerce, may be required to be submitted. The Administrator of EPA may even require that copies of these studies be submitted. This is one mechanism which might be employed in determining which completed studies will be included in the Directory.

3.4.2 CTSS Analysis and Evaluation File

The CTSS Analysis file, which will facilitate the independent evaluation of test data, requires test data to be in machine-readable form. This implies that test data submitted in hard copy will have to be converted to a tape format before they can be incorporated into the Analysis File. Although the submission of test data in a tape format is unlikely to be mandatory, the incentive to do so could be provided by granting access to the analytical capabilities of the CTSS file in order for laboratories to produce the required summary reports or to conduct detailed analyses of their test data.

The conversion of hard copy test data will be eased by the keying instructions and transaction formats which will be included on the worksheet. However, the sheer volume of studies will contribute to high conversion costs.

3.5 General Inquiry Subsystem

The CTSS Directory will fulfill the "current awareness" capability desired by users concerning information about animal studies. The establishment, maintenance, and access to the automated CTSS Directory will be supported by the General Inquiry Subsystem. Users would receive responses to queries covering a wide range of topics such as:

- The tests that have been conducted involving a particular chemical substance
- The status of a particular test
- The location of summary reports and/or detailed test data for a particular experiment

Since the CTSS Directory will act as a focal point for users within government and industry desiring "reference" information about animal studies, potential users indicated that it should cite as many studies as possible. Therefore the Directory shall encompass selected studies that have already been completed as well as those in progress, or are being planned by government agencies, research organizations, and industrial and independent laboratories.

The need to know about as many of the tests as possible requires that confidential as well as non-confidential tests be included in the Directory. Since the Directory will only reference an experiment and will not reveal the details of proprietary test data, inclusion in the Directory will not violate any confidentiality requirements. Users identifying a confidential test through the Directory would have to contact the appropriate "owner" of the test data to gain access to the desired material. The "owner" would then be in a position to grant access to appropriate users.[1] Certainly, the simple knowledge that a company is conducting a particular test may be considered confidential; and when there is no authority requiring the reporting of a test in progress, industry's proprietary information can be protected by omitting all references to it.

3.5.1 Data Elements

The data elements associated with the CTSS Directory will provide the user with the information required to identify, summarize, and locate laboratory studies. Table 3-2 identifies a list of data elements, proposed by Sigma

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[1] Many of the confidentiality considerations for test data reporting are addressed by EPA/OTS in their development of a Chemicals in Commerce Information System (CICIS).

TABLE 3-2
DATA ELEMENTS COMPRISING THE CTSS DIRECTORY

Element Name	Printable	Searchable
Test Substance	X	X
CAS Registry Number	X	X
Organization Conducting Test	X	X
Address of Laboratory	X	
Laboratory Internal Experiment Number	X	X
Principal Person Responsible for Test	X	X
Type of Experiment	X	X
Species	X	X
Start Date of Experiment	X	X
End Date of Experiment	X	X
Status of Experiment	X	X
Location of Test Data		
• Organization	X	X
• Contact Person/Telephone Number	X	
• Internal Accession Number	X	
IRLG-GLP Testing Guidelines	X	X

Data, that should be included in the CTSS Directory. Each data element is discussed below:

Test Substance - Identifies the chemical substance or substances that were tested. The test substance may include a single chemical, a mixture, or an industrial product. Included in the test substance identification would be chemical names, CAS preferred names, synonyms, and/or trade names.

CAS Registry Number - A unique 9-digit number is assigned by Chemical Abstracts Service to identify a chemical substance. The CAS registry number will provide the common access capability recommended for data bases included in the Chemical Substances Information Network (CSIN).

Name of Laboratory Conducting Test - The name of the laboratory that conducted the experiment and where it conducted the experiment and where the orginal "raw" test data are stored.

Address of Laboratory - Complete address including phone number of the laboratory that conducted the experiment.

Laboratory Internal Experiment Number - The code used by the laboratory conducting the study to identify the experiment. This would aid the user in locating specific test data stored at the laboratory.

Principal Person Responsible for Test - The name and phone number of the person who directed the experiment. This person may be contacted by users requiring additional information about the experiment.

Type of Experiment - A set of codes indicating what kind of study was conducted; i.e., acute dermal, subchronic inhalation, reproduction, teratogenicity, etc.

Species - A set of codes which would identify the organism used in the study.

Start Date of Experiment - The month, day, and year that the animals were first exposed to the test substance.

End Date of Experiment - The month, day, and year in which the last animal was taken off the experiment.

Status of Experiment - A code indicating whether the study has been completed, is currently being conducted or is being planned.

Location of Test Data - Indicates sources other than the laboratory that conducted the test where summary reports and/or detailed test data may be obtained. The locations might include the regulatory agency that received the data submission "package", another research organization, or the central facility for the CTSS analysis files (Section 3.6). This would also indicate to the user why the test might have been done, including the legislative and regulatory mandate(s). Included in the location would be the name and telephone number of the office or person to contact in order to obtain the data, and the internal accession number used at the particular location to identify the experiment.

IRLG-GLP Guidelines - Indicates whether the study was conducted and reported according to standardized predefined guidelines specified by the IRLG and GLPs.

If short-term test data or environmental studies are to be included in the CTSS Directory, additional data elements, noting bacteria and/or tissue cultures, and atmospheric or aquatic effects, will be necessary.

3.5.2 Maintenance and Update

The update of the CTSS Directory will involve active rather than passive procedures. This means that the organization responsible for the Directory cannot rely on voluntary submissions to build and maintain the data base, but it must actively monitor organizations such as Federal agencies and research laboratories that should be supplying information for the Directory. Appropriate offices within these organizations would be provided with data input forms. Periodically (a monthly schedule would be appropriate), the forms would be sent to the agency or contractor responsible for updating the Directory.

3.5.3 Search and Retrieval Capabilities

The searchable data elements in the CTSS Directory will include those indicated as such in Table 3-2.

Users will be able to combine these data elements to form a complex query. For instance, the user might want to know what acute inhalation studies for a particular test substance are being conducted and are following the IRLG-GLP guidelines.

The results of each query will be a list of the experiments which satisfy the search criteria. The user will have the option of specifying which data elements (Table 3-2) are to be displayed for the experiments that are retrieved.

Because a majority of users will be management or scientific personnel, a user interface must be designed which will require no prior knowledge of the Directory or of automated search and retrieval techniques in order to use the system effectively. Appropriate "help" and "explanation" facilities that respond to processing and informational problems will be available to the user. For example, these facilities will display a description of the individual data elements of the CTSS Directory, and a description of each of the available commands used for search and retrieval.

3.5.4 User Access

Because the CTSS was defined by the Mitre Report as a core component of the Chemical Substances Information Network and because the CTSS Directory is the key to the contents of the CTSS Analysis File, it would be appropriate for the Directory to be linked with at least two other CSIN components: the Chemical Data Bases Directory, and the Chemical Structure and Nomenclature System. (These are discussed further in Section 4.4). Exactly how these systems are to be linked in addition to other data bases, such as CICIS, LADB, and RTECS (Registry of Toxic Effects) is a primary objective of a contract between CEQ, EPA, the National Library of Medicine (NLM), and the Computer Corporation of America. Nonetheless, it is safe to say that the CTSS Directory should be widely and easily available and accessible to potential users.

3.6 Detailed Analysis and Evaluation Subsystem

A primary objective of the CTSS will be to provide investigators with the capability of retrieving selected information from particular studies in order to conduct independent evaluations. This function can be filled by a Detailed Analysis and Evaluation Subsystem which would facilitate test data evaluation in both on-line and batch modes. The system also should provide procedures for safeguarding confidential test data which are submitted in response to regulatory agency requirements.

3.6.1 Subject Matter, Scope, and Data Elements

The Analysis File will process and store the detailed test data that are collected for experiments conducted in accordance with the IRLG-GLP guidelines. Input to the Analysis File should be the data specified on the machine-readable transactions that would be recorded on the magnetic tapes discussed in Section 3.3.2. The data elements included in the CTSS Analysis File will therefore be those that are identified for each type of transaction.

No attempt should be made to analyze test data for experiments which were completed prior to system implementation. An undertaking of this kind, conducted by Technassociates, encountered difficulties which include the omission of critical data, different coding conventions, and the need for professional judgments in resolving "unique" observations. Each of these problems contributed to making the best data unreliable and inconsistent. By limiting the information in the CTSS Analysis File to data collected in a consistent, standardized manner, the integrity of the system will be maintained. Although the CTSS Analysis File cannot be established until the IRLG-GLP guidelines are utilized in animal studies, the long-term benefits will be increased in reliability and usefulness.

3.6.2 Maintenance and Update

The CTSS Analysis File should consist of a library of test data on magnetic tapes, and a similar on-line library of test data.

The tape library should consist of all the machine-readable test data on tapes that are received from the various regulatory agencies or research organizations for inclusion in the Detailed Analysis and Evaluation subsystem. A catalog should be maintained indicating what animal studies are available for the on-line Analysis File. Procedures should be established to notify the CTSS Directory of the availability of detailed test data through the CTSS Analysis File.

The on-line library should be a subset of the tape library and should consist of those animal studies that are stored on disks for immediate response to user queries. Before analyzing an animal study, users will query the CTSS Analysis File to determine if the test data is available on-line. If not, the user must request that the required test data be transferred from the tape library to the on-line library. There are four reasons for this: (a) test data for some studies can be quite voluminous. If all the information for all studies were on-line at all times, the disk capacity of the file would soon be exhausted as the number of studies increase; (b) only certain tests will require analysis at any particular time. The on-line library will contain studies that are currently "hot" issues; (c) the tape library will provide a convenient "back-up" for the Detailed Analysis and Evaluation on-line capability: (d) off-line storage would insure greater security for proprietary data.

Maintenance procedures should be developed for the on-line file capability which should be consistent with the limitations of the total, available systems resources.

3.6.3 Search and Retrieval Capabilities

Each data element in the system should be identified with an English-like mnemonic which can be used in a query. The query would consist of a series of data groups that are combined using logical connectors (AND, OR, NOT). A data group would consist of a data element and its relationship to a specific value. The relationship would include operatives such as equal to, less than, greater than, not equal to, etc. The user would be able to compare data across multiple experiments or confine analysis to a small subset of a single experiment.

Several options would be available for output:

(a) predefined reports which represent a set of frequently used display formats (such as the summary reports discussed in Section 3.3.3)

(b) Specification of individualized reports with selected data items, report headings, sorting, and ranking. "Save" files should be available to permit the storage of frequently used queries or report formats. This would eliminate the keying in of specifications at the terminal every time they were needed. In addition, a user could alter a "save" file (data elements or operatives) at the time of execution.

(c) graphic displays, either from predefined specifications or user-specified requirements, which would include scatter plots, polygon plots, bar charts, polynomial fits, and multi-variable plots.

As indicated in the IRLG-GLP guidelines, an evaluation of scientific data such as animal study information will require the capability of statistical analysis. Some of the statistical analyses indicated in the IRLG-GLP guidelines are provided by commercial statistical packages include linear and non-linear regression analyses, variance and covariance analyses, time series analysis, t-tests, and goodness-of-fit tests.

A batch processing capability will be provided to produce reports that would be too long and time-consuming to print at a terminal or which take too long to process. Users would specify the required parameters at a terminal; the output would be printed off-line and sent to the user.

3.6.4 User Access

Users involved in data evaluation indicated that analyses are best accomplished by direct access to the data as opposed to an intermediary between the system and the analyst. Interaction with the CTSS Analysis File should be through on-line terminals, either graphic types for maximum capability or less expensive TTY-compatible terminals.

To respond to the potential user community, the CTSS should be available through the Chemical Substances Information Network in order to facilitate linkages with other CSIN components which are deemed appropriate.[1] Regardless of what network configuration is selected, consideration must be given to developing compatibility, if not direct linkage, with the Chemical Structure/Nomenclature System (CSNS). The chemical identification function of the CSNS would be closely connected to the chemical evaluation function (toxicity, carcinogenicity, mutagenicity, etc.,) which will be performed by the CTSS Analysis File. A similar consideration should be directed towards LADB and its relevance to the functions of the CTSS. In addition, CTSS shall be referenced or registered in the Chemical Data Bases Directory (CDBD). (CSIN is discussed further in Section 4.4)

There are at least two viable options for the location of the Analysis File, either at a central facility or duplication at satellite facilities. The greatest concern will be for studies which are considered confidential. If all data are stored at a central facility, security mechanisms should be included for protecting the tape library as well as for controlling the on-line file with encryption codes. If the software is to be transferred to other facilities, the transfer requires either identical computer systems or conversion programs to adapt the software to other systems. Duplication of the software for different computer systems would involve substantial development costs.

3.6.5 File Organization Structure

Since immediate response to user queries will be emphasized in the CTSS Analysis File, the file organization and structure techniques should accommodate rapid search and retrieval of data. The anticipated large volume of on-line data would indicate that computer dependent organizational characteristics that increase processing speeds should be employed.

The CTSS Analysis File may be organized into several levels of data. The highest level would consist of data for a particular animal study. The next level would include the functional groups of data within an experiment, i.e. the various transactions recorded on magnetic tape (Section 3.3.2); and the lowest level would include the various data elements for a functional group or transaction. The data included in the various levels would be dynamic rather than static. New transaction types would be added as guidelines for additional types of animal studies are developed. Similarly, additional data elements may be defined for existing transactions. A file organization that utilized "table driven" techniques would accommodate this situation. Under this technique, the characteristics of the various transactions and associated data elements are defined in a table or series of tables. As the CTSS Analysis File is being created, the table is used by the software package to transform the transactions on magnetic tape into the appropriate on-line file organization on disc packs in a generalized manner. When changes are required the table is modified, not the computer software. Therefore the time consuming and expensive process of modifying and re-testing existing software would be eliminated.

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[1] A contract has been negotiated with Computer Corportion of America to define the specific user requirements which will assist in determining the precise network design and configuration.

Search and retrieval capabilities for the CTSS Analysis File require that a capability exist for each data element to participate in a query specification. Maximum search and retrieval speed would be achieved by organizing the file such that all data elements were indexed. However, in the case of the CTSS Analysis File, the large number of data elements and the amount of storage required for the indices would prohibit such an action. Instead, an index capability would be developed for data elements that are most often employed in a search or retrieval query. Such data elements might include group identification, animal identification, dose level, clinical signs, animal organ, necropsy findings, and histopathological findings. In this way queries would be satisfied by first accessing data elements that are indexed and then constructing a sequential search to satisfy data elements that are not indexed.

4.0 EXISTING CAPABILITIES

4.1 Approach and Scope

The proposed design requirements for the Chemical Testing Support System presented in Section 3.0 represent an idealized version of a system to collect and disseminate laboratory animal testing data. This section presents the results of a survey and an evaluation of existing capabilities to determine to what extent they could be incorporated into the CTSS.

A preliminary analysis of existing capabilities indicates that they fall into two general categories, identification of animal tests, and acquisition and analysis of animal test data. The identification of animal tests pertains to the General Inquiry subsystem. Whereas the animal test data acquisition and analysis is related to the Data Collection, Data Submission, Storage and Conversion, and Detailed Analysis and Evaluation subsystems because data collected must correspond to the data submitted which in turn must correspond to the data that are analyzed.

4.2 Directory of Animal Tests

Users indicated that they currently consult certain data bases to obtain citation information, but expressed concern that they might be missing information in decisionmaking.

Based on these user comments, Sigma Data surveyed several existing services that would satisfy the needed capabilities:

- MEDLARS Bibliographic Reference System
- National Technical Information Service (NTIS)
- Smithsonian Science Information Exchange (SSIE)
- TOX-TIPS (Toxicology Testing in Progress)
- Toxicology.Research Projects Directory

4.2.1 MEDLARS Bibliographic Reference System

MEDLARS (Medical Literature Analysis and Retrieval System) provides on-line access to a number of bibliographic data bases that are constructed and maintained by the National Library of Medicine. Users communicate with the MEDLARS files through a computer terminal connected by a direct phone line to the computer facility in Bethesda, Maryland, or via a nationwide time-sharing network with access nodes located in major cities. MEDLARS is currently available at approximately 280 organizations including academic, commercial and government agencies.

CTSS users would find MEDLARS useful for obtaining citations and abstracts relating to animal studies that have been completed and published in a wide variety of journals. Relevant MEDLARS data bases include MEDLINE, SDILINE, TOXLINE and CANCERLINE. A description of current cancer research projects can be found in CANCERPROJ.

Users wishing to access MEDLARS must subscribe to the service through NLM or utilize one of the on-line centers already subscribing to MEDLARS. The cost for searching the data bases varies from $8 to $15 per terminal connect hour, depending on the time of day. There is also a charge of $.10 for each page of off-line printout.

All of the MEDLARS data bases can be accessed using the same search and retrieval language at the same terminal session. The bibliographic data bases all contain citation information that would be useful to a potential CTSS user. Most of the data elements are searchable including author, title, abstract, journal source, and year of publication. MEDLINE also uses a controlled vocabulary known as MESH (Medical Subject Headings) which are also searchable.

Citations and/or abstracts may be printed on-line at the user's terminal or off-line and mailed to the user. Users may select a print format varying from a brief identification of author, title, and source to a complete listing of bibliographic record, including the abstract.

Each data base is described in more detail below:

MEDLINE - This file contains over 600,000 references to biomedical journal articles published in the current and two preceeding years. Article citations are derived from over 3,000 journals and serials published in the U.S. and 70 foreign countries. Selected monographs are also included in MEDLINE. Coverage of previous years (back to 1966) is provided by off-line historical files containing nearly 2 million references.

SDILINE - Users that want to search only the recent additions to the MEDLINE file can search a subfile known as SDILINE. Journals and serials put into MEDLINE for the current month are also entered in SDILINE. The file contains approximately 20,000 citations and the entire data base is replaced each month.

TOXLINE - This file is a collection of over 380,000 references from the last five years of published human and animal toxicity studies, effects of environmental chemicals and pollutants, and adverse drug reactions. Older material is retrievable from an historical file called TOXBACK. The references are from five major published secondary sources and three special literature collections maintained by other government agencies.

TOXLINE can be directly searched by a chemical substance using the associated CAS Registry Number. This number can be obtained from the on-line chemical identification dictionary known as CHEMLINE which is also part of MEDLARS. Figure 4-1 illustrates the data elements comprising a TOXLINE file record.

CANCERLINE - This file is sponsored by NIH's National Cancer Institute and contains more than 85,000 references related to cancer. Over 3,000 U.S. and foreign journals, as well as selected monographs, scientific papers, reports, and dissertations are abstracted for inclusion in CANCERLINE. Figure 4-2 illustrates the data elements comprising a CANCERLINE file record.

CANCERPROJ - This data base provides users with summaries of cancer research projects in progress which have been provided by scientists in the U.S and foreign countries. The file contains over 16,000 descriptions covering the current and two preceeding years. The data for project descriptions are processed by the Current Cancer Research Projects Analysis Center of the International Cancer Research Data Bank Program located at the Smithsonian Science Information Exchange. The summaries include work being done by federally and privately supported grants and contracts. Figure 4-3 illustrates the data elements included in the file, and Figure 4-4 illustrates a project description retrieved from the CANCERPROJ file.

4.2.2 National Technical Information Service (NTIS)

The National Technical Information Service is an organization within the U.S. Department of Commerce that collects and sells reports and analyses prepared by Federal agencies, their contractors, or grantees. Reports are received

FIGURE 4-1

TOXLINE Data Elements

UNIT RECORD DESCRIPTION:

ABBREV	CATEGORY NAME	SEARCH STATUS	PRINT	PRINT FULL	PRINT DETAILED
(SI)	SEC SOURCE ID (IE HEEP/74/05412)	YES	YES	YES	YES
(AU)	AUTHOR(S) (IE HAYES WJ)	YES	YES	YES	YES
(AA)	AUTHOR ADDRESS	NO	NO	YES	YES
(TI)	ARTICLE TITLE (STRINGSEARCHABLE; UNIQUE WORDS ARE IN TEXT; SEE TW)	NO	YES	YES	YES
(LA)	LANGUAGE	YES	NO	YES	YES
(JC)	JOURNAL CODEN	YES	NO	NO	YES
(IS)	INTL STAND SER NO	YES	NO	NO	YES
(SO)	SOURCE JOURNAL/CITATION	NO	YES	YES	YES
(AB)	ABSTRACT (STRINGSEARCHABLE; UNIQUE WORDS ARE IN TEXT, SEE TW)	NO	NO	YES	YES
(RN)	CHEM ABSTR (CAS) REG NO.(143-50-0)	YES	NO	NO	YES
(IT)	INDEX TAG (ON CBAC SINCE NOV. 76)	YES	NO	NO	YES
(DT)	DATA TAG (ON CBAC SINCE NOV. 76)	YES	NO	NO	YES
(TW)	TEXT WORDS (UNIQUE WORDS FROM TITLE, ABSTRACT AND KEYWORDS)	YES	NO	NO	NO
(YP)	YR PRIMARY JNL (2 DIGITS,EG 75)	YES	NO	NO	NO
(ST)	SOURCE AND TIME FRAME UPDATE TAG (IE 7804 FOR 1978 APRIL UPDATE)	YES	NO	NO	NO
(KW)	KEYWORDS (TEXTRACTED UNITERMS FROM TI, KW)	YES	NO	NO	NO
KW	KEYWORDS (UNIQUE WORDS ARE IN TEXT; SEE TW), FROM IPA, TOXBIB, ETC.	NO	NO	NO	YES

FIGURE 4-2

CANCERLINE Citation From MEDLARS

```
SOURCE IDENTIFIER          CARC/78/00641
AUTHOR                     Schmoldt A
AUTHOR                     Altenahr E
AUTHOR                     Grote W
AUTHOR                     Dammann HG
AUTHOR                     Sidau B
AUTHOR                     Benthe HF
ADDRESS                    Dept. Pharmacology, Martinistr. 52, D-2000
                           Hamburg 20, W. Germany
TITLE                      RAT LIVER CHANGES AFTER SUBCHRONIC EXPOSITION
                           TO POLYCHLORINATED BIPHENYLS (PCB) OF LOW
                           CHLORINE CONTENT.
ENTRY DATE                 7801
SOURCE                     Arch Toxicol (Berl); 37(3):203-217 1977
LANGUAGE                   ENG
JOURNAL CODEN              ATXKA
INTL STAND SER NO          0003-9446
ABSTRACT                   A commercial polychlorinated biphenyl (PCB)
                           mixture, Clophen A30 with 42% chlorine
                           [trichlorobiphenyl (triCB-5)] and two
                           purified products with 2% and 0.4% highly
                           chlorinated biphenyls (triCB-2 and triCB-0.4,
                           respectively) were administered in subchronic
                           doses to male Wistar rats and the liver
                           changes examined. The animals received the
                           PCBs at 2000 ppm in the diet for 12 wk. The
                           body wt of the PCB-treated rats was reduced,
                           but the liver wt was increased; the general
                           structure of the liver was preserved,
                           however. The most noticeable effect, apparent
                           in all animals, was cytoplasmic clumping and
                           the occurrence of annular inclusion bodies in
                           the cytoplasm. Electron microscopy revealed a
                           proliferation of the tubular and vesicular
                           smooth endoplasmic reticulum (SER).
                           Mitochondria were also displaced but most
                           were intact; however, in two rats exposed to
                           triCB-5 for 9 wk, hydropically swollen and
                           bizarrely shaped mitochondria were noted. In
                           acute experiments with 1.7 millimole/kg diCB,
                           tetraCB or hexaCB, it was noted that the
                           increased liver wt was due to cell
                           hypertrophy. After subchronic exposure, SGOT
                           and SGPT activities were normal, but plasma
                           elimination of sulfobromophthalein was
                           increased; elevated phospholipid values
                           correlated with SER proliferation. triCB-5
                           produced the highest induction of the
                           microsomal monooxygenases, but the other
                           effects of the triCBs were equal. Porphyria
                           induction by all compounds was probably due
                           to decarboxylation inhibition. The content of
                           triCB-5 in the livers exceeded that of the
                           other two triCBs but the difference was not
                           significant. It is concluded that low
                           chlorinated PCBs have a lower hepatotoxicity
                           than those with high chlorine content. (31
                           Refs)
YEAR OF PUBLICATION        77
JOURNAL TITLE              Arch Toxicol (Berl)
PUBLICATION TYPE           Journal Article
```

Reproduced from
best available copy.

FIGURE 4-4

CANCERPROJ Citation From MEDLARS

Reproduced from best available copy.

TITLE	LONG-TERM, LOW-LEVEL EXPOSURE TO ENVIRONMENTAL AGENTS (HUMAN, MICE)
INVESTIGATORS	SELIKOFF IJ
LOCATION	CITY UNIVERSITY OF NEW YORK; SCHOOL OF MEDICINE; COMMUNITY MEDICINE; 5TH AVE. AT E. 100TH ST.; NEW YORK, NEW YORK 10029
ABSTRACT	This project is part of a broader program (ES 00928-04) whose summary states: The planned research program for 1976-1977 of the Environmental Health Sciences Center includes the continuation of the principal lines of research established four years ago and the mounting of a number of new research projects. The principal categories of these studies include (a) human health effects, (b) low-level, long-term exposure to environmental agents, (c) asbestos health effects, (d) multiple factor interactions, (e) biological properties of inorganic microparticles, (f) environmental cancer. The methodological perspectives include interdisciplinary and, sometimes, inter-institutional collaboration, epidemiological approaches, utilization of cohorts of (employed) groups exposed to defined environmental influences. 110 research projects are detailed and include investigation of the health effects of a variety of environmental agents including lead, polychlorinated biphenyls, polybrominated biphenyls, nitrosamines, asbestos, solvents, titanium, polycyclic aromatic hydrocarbons, printing dyes, styrene, vinyl chloride, silica, silicates, organic fibers, printing inks and dyes, amorphous silica, acrylonitrile, halothane, isoniazide, aniline dyes.|
ABSTRACT	BIBLIOGRAPHIC REFERENCES: Anderson, H. A., Lilis, R., Daum, S. M., Fischbein, A. S. and Selikoff, I. J. Household contact asbestos neoplastic risk. Ann. N.Y. Acad. Sci. 271:311-323, 1976. Berk, P. D., Martin, J. F., Young, R.S., Creech, J., Selikoff, I. J., Falk, H., Watanabe, P., Popper, H. and Thomas, L. Vinyl chloride-associated liver disease. Ann. Intern. Med. 84:717-731, 1976.
BEGIN DATE	7609
END DATE	7708
FISCAL YEAR	76
SUPPORTING AGENCY ID NO.	P30 ES 00928-040044
SUPPORTING AGENCY	U.S. Dept. of Health Education & Welfare; Public Health Service; National Inst. of Health; National Inst. of Environmental Health Sciences
TYPE OF AWARD	G
ACCESSION NUMBER	BQ 572 2
PERFORMING ORGANIZATION	CITY UNIVERSITY OF NEW YORK
COUNTRY - STATE	NEW YORK
COUNTRY - STATE	USA

from over 200 Federal agencies as well as some state and local government agencies. Frequently, they are the final reports of the research projects registered with the Smithsonian Science Information Exchange (see Section 4.2.3).

NTIS reports include material from all scientific disciplines. The multidisciplinary scope might be useful to CTSS users and includes work from the behavioral/social sciences, biological and medical sciences, toxicology, and environmental pollution and control research. NTIS compiles a comprehensive index and an abstract for each report which is available in hard copy as well as on-line. The hard copy version consists of a number of indexes including a subject, organization, and author index. The subject index enables CTSS users to search on a specific chemical substance by name. Figure 4-5 illustrates a portion of the subject index while Figure 4-6 illustrates a portion of the report citation section. The hard copy index is abailable through NTIS at $45 per year.

An on-line version of the index is available on three time-sharing networks, the System Development Corp. (SDC) Search Service, the Lockheed Information Systems, and the Bibliographic Retrieval Service, Inc. (BRS). These on-line services provide the user with a rapid access capability and a powerful and varied search capability. Figure 4-7 identifies the data elements associated with each citation in the NTIS data base available through the SDC network and indicates which data elements can be used in a query specification. Figure 4-8 illustrates a typical citation printout.

The cost to access the NTIS data base through the SDC network is $45 per terminal connect hour, plus $.08 per citation for off-line printing. Comparable rates are charged by the Lockheed network. The BRS network is less expensive, $23 per terminal connect hour. Once desired reports have been identified, they may be obtained from NTIS at a nominal charge, usually between $5 and $15.

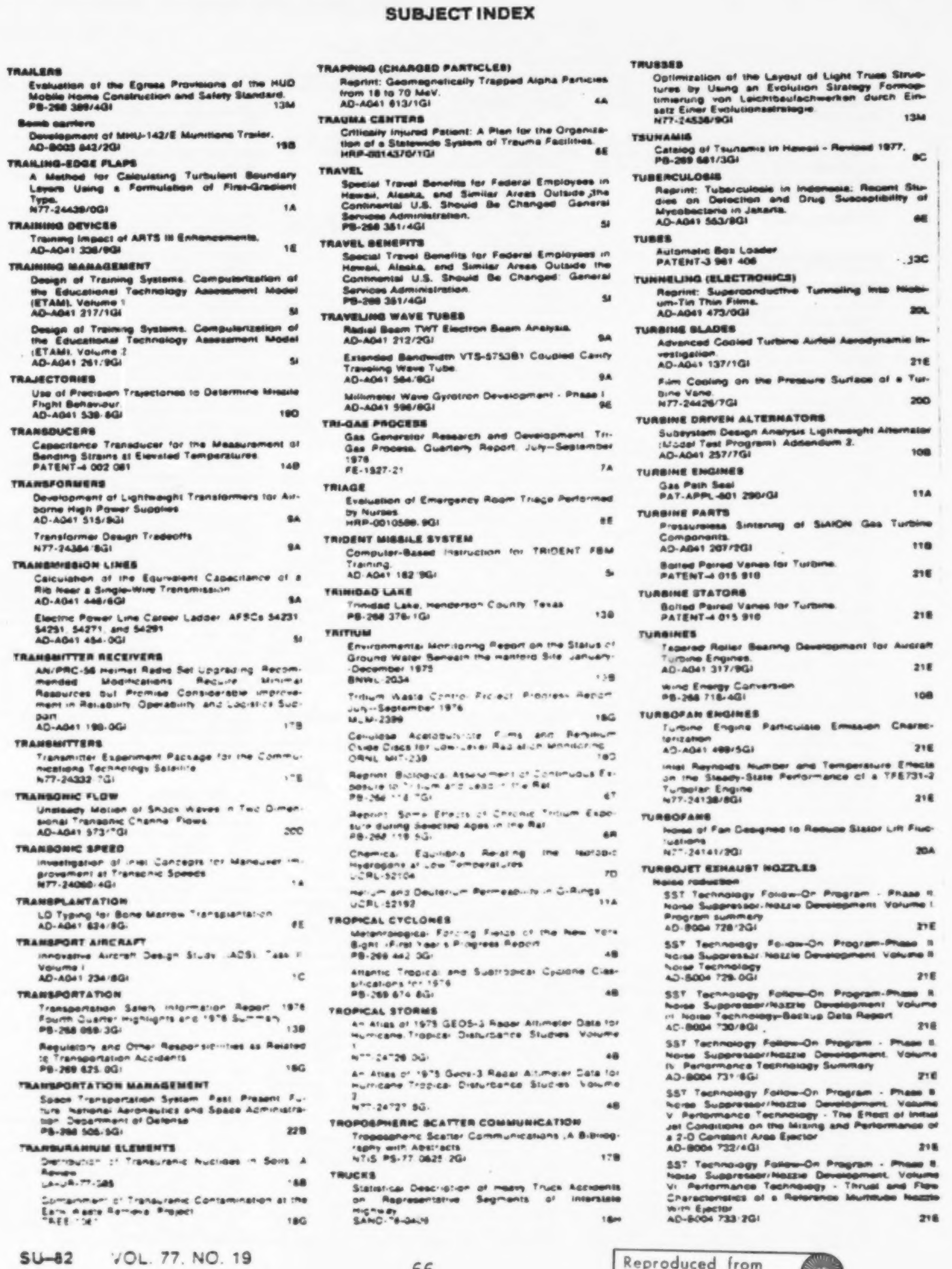
4.2.3 Smithsonian Science Information Exchange (SSIE)

The Smithsonian Science Information Exchange was established to help to plan and conduct research by gathering and exchanging information about current and recently completed investigations. SSIE processes information on more than 100,000 research projects each year in all areas of basic and applied research in the life and physical sciences. It serves as the major source for information on research in progress. This information is obtained on a monthly basis, from more than 1,300 Federal agencies, state, and local organizations, foundations, associations, colleges and universities, and foreign organizations.

By using SSIE, CTSS research investigators and managers of research programs could learn of a research project when it is initiated or planned and would not have to wait until the results are published. SSIE estimates they collect information on about 80% of the research projects sponsored by the Federal government; and in some agencies, 100% of the research projects are registered. Scientists performing research which might not be reported by funding organizations are encouraged to register their projects with SSIE.

FIGURE 4-5

NTIS Subject Index



SUBJECT INDEX

TRAILERS
Evaluation of the Egress Provisions of the HUD Mobile Home Construction and Safety Standard.
PB-268 389/4GI 13M
Bomb carriers
Development of MHU-142/E Munitions Trailer.
AD-B003 842/2GI 19B

TRAILING-EDGE FLAPS
A Method for Calculating Turbulent Boundary Layers Using a Formulation of First-Gradient Type.
N77-24439/0GI 1A

TRAINING DEVICES
Training Impact of ARTS III Enhancements.
AD-A041 336/9GI 1E

TRAINING MANAGEMENT
Design of Training Systems. Computerization of the Educational Technology Assessment Model (ETAM). Volume 1
AD-A041 217/1GI 5I
Design of Training Systems. Computerization of the Educational Technology Assessment Model (ETAM). Volume 2
AD-A041 261/9GI 5I

TRAJECTORIES
Use of Precision Trajectories to Determine Missile Flight Behaviour.
AD-A041 539/8GI 19D

TRANSDUCERS
Capacitance Transducer for the Measurement of Bending Strains at Elevated Temperatures
PATENT-4 002 061 14B

TRANSFORMERS
Development of Lightweight Transformers for Airborne High Power Supplies
AD-A041 515/8GI 9A
Transformer Design Tradeoffs
N77-24384/8GI 9A

TRANSMISSION LINES
Calculation of the Equivalent Capacitance of a Rib Near a Single-Wire Transmission
AD-A041 446/6GI 9A
Electric Power Line Career Ladder AFSCs 54231, 54251, 54271, and 54291
AD-A041 464/0GI 5I

TRANSMITTER RECEIVERS
AN/PRC-56 Helmet Radio Set Upgrading Recommended Modifications Require Minimal Resources but Promise Considerable Improvement in Reliability Operability and Logistics Support
AD-A041 190/0GI 17B

TRANSMITTERS
Transmitter Experiment Package for the Communications Technology Satellite
N77-24332/7GI 17B

TRANSONIC FLOW
Unsteady Motion of Shock Waves in Two Dimensional Transonic Channel Flows
AD-A041 573/7GI 20D

TRANSONIC SPEED
Investigation of Inlet Concepts for Maneuver Improvement at Transonic Speeds
N77-24080/4GI 1A

TRANSPLANTATION
LD Typing for Bone Marrow Transplantation
AD-A041 624/8GI 6E

TRANSPORT AIRCRAFT
Innovative Aircraft Design Study (IADS) Task II Volume I
AD-A041 234/6GI 1C

TRANSPORTATION
Transportation Safety Information Report 1976 Fourth Quarter Highlights and 1976 Summary
PB-268 069/3GI 13B
Regulatory and Other Responsibilities as Related to Transportation Accidents
PB-269 625/0GI 18G

TRANSPORTATION MANAGEMENT
Space Transportation System Past Present Future National Aeronautics and Space Administration Department of Defense
PB-268 506/5GI 22B

TRANSURANIUM ELEMENTS
Distribution of Transuranic Nuclides in Soils A Review
LA-UR-77-385 18B
Containment of Transuranic Contamination at the Early Waste Retrieval Project
TREE-[illegible] 18G

TRAPPING (CHARGED PARTICLES)
Reprint: Geomagnetically Trapped Alpha Particles from 18 to 70 MeV.
AD-A041 613/1GI 4A

TRAUMA CENTERS
Critically Injured Patient: A Plan for the Organization of a Statewide System of Trauma Facilities.
HRP-0014370/1GI 6E

TRAVEL
Special Travel Benefits for Federal Employees in Hawaii, Alaska, and Similar Areas Outside the Continental U.S. Should Be Changed General Services Administration.
PB-268 381/4GI 5I

TRAVEL BENEFITS
Special Travel Benefits for Federal Employees in Hawaii, Alaska, and Similar Areas Outside the Continental U.S. Should Be Changed: General Services Administration.
PB-268 381/4GI 5I

TRAVELING WAVE TUBES
Radial Beam TWT Electron Beam Analysis.
AD-A041 212/2GI 9A
Extended Bandwidth VTS-5753B1 Coupled Cavity Traveling Wave Tube.
AD-A041 584/8GI 9A
Millimeter Wave Gyrotron Development - Phase I
AD-A041 598/8GI 9E

TRI-GAS PROCESS
Gas Generator Research and Development. Tri-Gas Process. Quarterly Report. July—September 1976
FE-1527-21 7A

TRIAGE
Evaluation of Emergency Room Triage Performed by Nurses.
HRP-0010586/9GI 6E

TRIDENT MISSILE SYSTEM
Computer-Based Instruction for TRIDENT FBM Training.
AD-A041 182/9GI 5I

TRINIDAD LAKE
Trinidad Lake, Henderson County Texas
PB-268 376/1GI 13B

TRITIUM
Environmental Monitoring Report on the Status of Ground Water Beneath the Hanford Site January-December 1975
BNWL-2034 13B
Tritium Waste Control Project Progress Report July—September 1976
MLM-2399 18G
Cellulose Acetobutyrate Films and Beryllium Oxide Discs for Low-Level Radiation Monitoring
ORNL/MIT-239 18D
Reprint: Biological Assessment of Continuous Exposure to Tritium and Lead in the Rat
PB-268 118/7GI 6T
Reprint: Some Effects of Chronic Tritium Exposure during Selected Ages in the Rat
PB-268 119/5GI 6R
Chemical Equilibria Relating the Isotopic Hydrogens at Low Temperatures
UCRL-52104 7D
Helium and Deuterium Permeability in O-Rings
UCRL-52192 11A

TROPICAL CYCLONES
Meteorological Forcing Fields of the New York Bight (First Year's Progress Report)
PB-268 442/3GI 4B
Atlantic Tropical and Subtropical Cyclone Classifications for 1976
PB-269 674/8GI 4B

TROPICAL STORMS
An Atlas of 1975 GEOS-3 Radar Altimeter Data for Hurricane/Tropical Disturbance Studies. Volume 1
N77-24726/3GI 4B
An Atlas of 1975 Geos-3 Radar Altimeter Data for Hurricane/Tropical Disturbance Studies. Volume 2
N77-24727/5GI 4B

TROPOSPHERIC SCATTER COMMUNICATION
Tropospheric Scatter Communications (A Bibliography with Abstracts)
NTIS/PS-77/0625/2GI 17B

TRUCKS
Statistical Description of Heavy Truck Accidents on Representative Segments of Interstate Highway
SAND-76-0429 16M

TRUSSES
Optimization of the Layout of Light Truss Structures by Using an Evolution Strategy Formoptimierung von Leichtbaufachwerken durch Einsatz Einer Evolutionsstrategie
N77-24536/9GI 13M

TSUNAMIS
Catalog of Tsunamis in Hawaii - Revised 1977.
PB-269 681/3GI 8C

TUBERCULOSIS
Reprint: Tuberculosis in Indonesia: Recent Studies on Detection and Drug Susceptibility of Mycobacteria in Jakarta.
AD-A041 563/9GI 6E

TUBES
Automatic Box Loader
PATENT-3 981 406 13C

TUNNELING (ELECTRONICS)
Reprint: Superconductive Tunneling into Niobium-Tin Thin Films.
AD-A041 473/0GI 20L

TURBINE BLADES
Advanced Cooled Turbine Airfoil Aerodynamic Investigation.
AD-A041 137/1GI 21E
Film Cooling on the Pressure Surface of a Turbine Vane.
N77-24426/7GI 20D

TURBINE DRIVEN ALTERNATORS
Subsystem Design Analysis Lightweight Alternator (Model Test Program) Addendum 2.
AD-A041 257/7GI 10B

TURBINE ENGINES
Gas Path Seal
PAT-APPL-801 290/GI 11A

TURBINE PARTS
Pressureless Sintering of SiAlON Gas Turbine Components.
AD-A041 207/2GI 11B
Bolted Paired Vanes for Turbine.
PATENT-4 015 910 21E

TURBINE STATORS
Bolted Paired Vanes for Turbine.
PATENT-4 015 910 21E

TURBINES
Tapered Roller Bearing Development for Aircraft Turbine Engines.
AD-A041 317/9GI 21E
Wind Energy Conversion
PB-268 718/4GI 10B

TURBOFAN ENGINES
Turbine Engine Particulate Emission Characterization
AD-A041 499/5GI 21E
Inlet Reynolds Number and Temperature Effects on the Steady-State Performance of a TFE731-2 Turbofan Engine
N77-24138/8GI 21E

TURBOFANS
Noise of Fan Designed to Reduce Stator Lift Fluctuations
N77-24141/2GI 20A

TURBOJET EXHAUST NOZZLES
Noise reduction
SST Technology Follow-On Program - Phase II. Noise Suppressor/Nozzle Development. Volume I. Program summary
AD-B004 728/2GI 21E
SST Technology Follow-On Program-Phase II. Noise Suppressor/Nozzle Development. Volume II. Noise Technology
AD-B004 729/0GI 21E
SST Technology Follow-On Program-Phase II. Noise Suppressor/Nozzle Development. Volume III. Noise Technology-Backup Data Report
AD-B004 730/8GI 21E
SST Technology Follow-On Program - Phase II. Noise Suppressor/Nozzle Development. Volume IV. Performance Technology Summary
AD-B004 731/6GI 21E
SST Technology Follow-On Program - Phase II. Noise Suppressor/Nozzle Development. Volume V. Performance Technology - The Effect of Initial Jet Conditions on the Mixing and Performance of a 2-D Constant Area Ejector
AD-B004 732/4GI 21E
SST Technology Follow-On Program - Phase II. Noise Suppressor/Nozzle Development. Volume VI. Performance Technology - Thrust and Flow Characteristics of a Reference Multitube Nozzle with Ejector
AD-B004 733/2GI 21E

SU—82 VOL. 77. NO. 19

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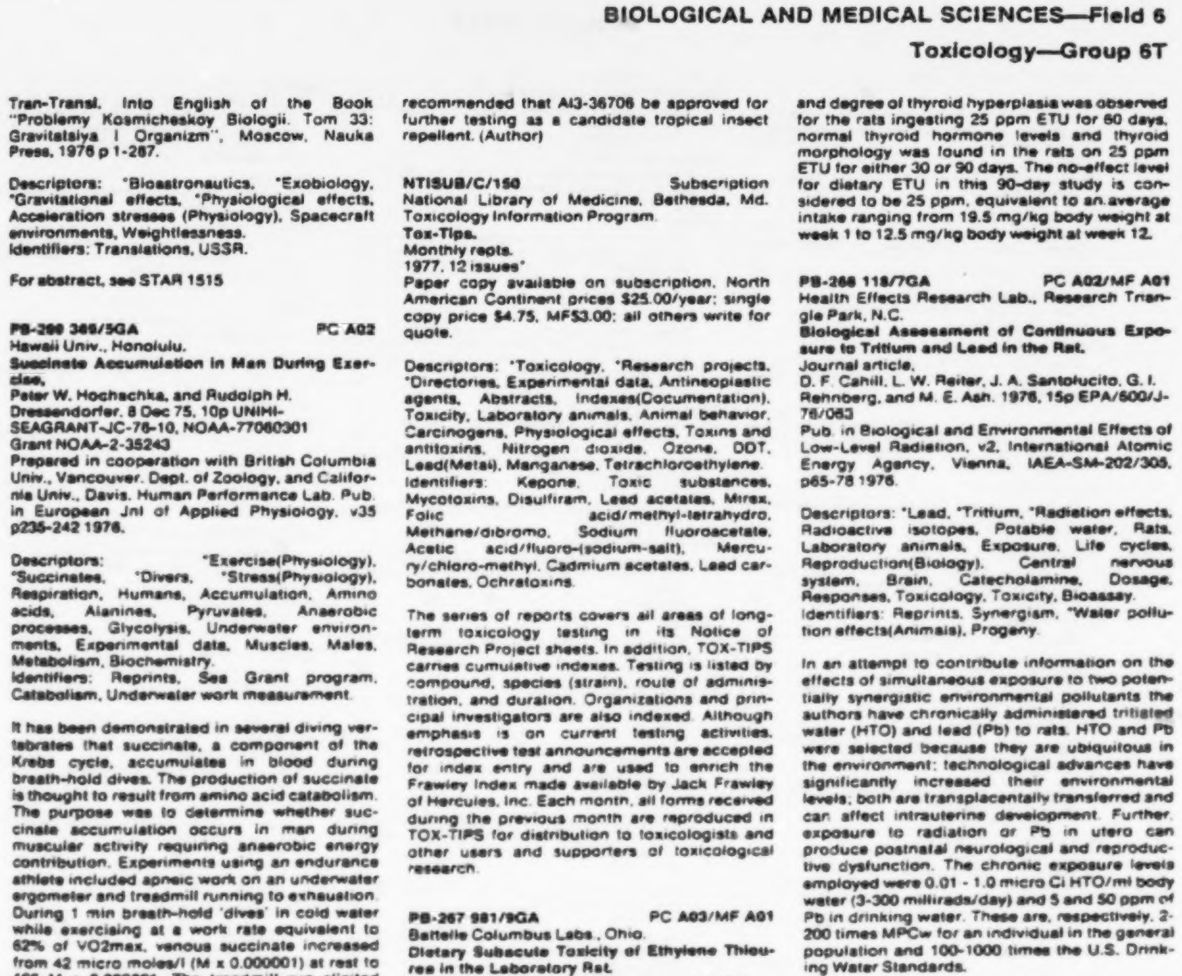
FIGURE 4-6

NTIS Report Citation



BIOLOGICAL AND MEDICAL SCIENCES—Field 6

Toxicology—Group 6T

Tran-Transl. into English of the Book "Problemy Kosmicheskoy Biologii. Tom 33: Gravitatsiya I Organizm", Moscow, Nauka Press, 1976 p 1-287.

Descriptors: *Bioastronautics, *Exobiology, *Gravitational effects, *Physiological effects, Acceleration stresses (Physiology), Spacecraft environments, Weightlessness.
Identifiers: Translations, USSR.

For abstract, see STAR 1515

PB-260 369/5GA **PC A02**
Hawaii Univ., Honolulu.
Succinate Accumulation in Man During Exercise,
Peter W. Hochachka, and Rudolph H. Dressendorfer. 8 Dec 75, 10p UNIHI-SEAGRANT-JC-76-10, NOAA-77060301
Grant NOAA-2-35243
Prepared in cooperation with British Columbia Univ., Vancouver. Dept. of Zoology, and California Univ., Davis. Human Performance Lab. Pub. in European Jnl of Applied Physiology, v35 p235-242 1976.

Descriptors: *Exercise(Physiology), *Succinates, *Divers, *Stress(Physiology), Respiration, Humans, Accumulation, Amino acids, Alanines, Pyruvates, Anaerobic processes, Glycolysis, Underwater environments, Experimental data, Muscles, Males, Metabolism, Biochemistry.
Identifiers: Reprints, Sea Grant program, Catabolism, Underwater work measurement.

It has been demonstrated in several diving vertebrates that succinate, a component of the Krebs cycle, accumulates in blood during breath-hold dives. The production of succinate is thought to result from amino acid catabolism. The purpose was to determine whether succinate accumulation occurs in man during muscular activity requiring anaerobic energy contribution. Experiments using an endurance athlete included apneic work on an underwater ergometer and treadmill running to exhaustion. During 1 min breath-hold 'dives' in cold water while exercising at a work rate equivalent to 62% of VO2max, venous succinate increased from 42 micro moles/l (M x 0.000001) at rest to 125 M x 0.000001. The treadmill run elicited VO2max and increased succinate from a similar resting value to 93 M x 0.000001. Increases in alanine, lactate, and pyruvate were observed for both types of exercise. The findings confirm that succinate accumulation also occurs in man. It was suggested that amino acid catabolism may provide a source of anaerobic energy production in addition to glycolysis. However, the importance of the proposed energy pathway remains to be quantified.

6T. Toxicology

AD-A041 060/5GA **PC A02/MF A01**
Army Environmental Hygiene Agency Aberdeen Proving Ground Md
Topical Hazard Evaluation Program of Candidate Insect Repellent AI3-36706 Pentyl 2-Aminobenzoate.
Final rept. Mar 76-Apr 77,
Maurice H. Weeks, and Brenda J. DeSena. 27 Jun 77, 8p Rept no. USAEHA-51-0847-77

Descriptors: *Insect repellents, Toxicity, Amines, Rats, Rabbits, Guinea pigs, Irritation, Skin(Anatomy), Eye, Oral dosage, Sensitizing, Photochemical reactions.
Identifiers: Benzoate/pentyl 2-amino, Laboratory animals, Bioassay.

A hazard evaluation of the candidate insect repellent AI3-36706, pentyl 2-aminobenzoate, was performed by means of laboratory animal studies using rats, rabbits and guinea pigs. Based on findings from these studies it is recommended that AI3-36706 be approved for further testing as a candidate tropical insect repellent. (Author)

NTISUB/C/150 Subscription
National Library of Medicine, Bethesda, Md. Toxicology Information Program.
Tox-Tips.
Monthly repts.
1977, 12 issues*
Paper copy available on subscription. North American Continent prices $25.00/year; single copy price $4.75, MF$3.00; all others write for quote.

Descriptors: *Toxicology, *Research projects, *Directories, Experimental data, Antineoplastic agents, Abstracts, Indexes(Documentation), Toxicity, Laboratory animals, Animal behavior, Carcinogens, Physiological effects, Toxins and antitoxins, Nitrogen dioxide, Ozone, DDT, Lead(Metal), Manganese, Tetrachloroethylene.
Identifiers: Kepone, Toxic substances, Mycotoxins, Disulfiram, Lead acetates, Mirex, Folic acid/methyl-tetrahydro, Methane/dibromo, Sodium fluoroacetate, Acetic acid/fluoro-(sodium-salt), Mercury/chloro-methyl, Cadmium acetates, Lead carbonates, Ochratoxins.

The series of reports covers all areas of long-term toxicology testing in its Notice of Research Project sheets. In addition, TOX-TIPS carries cumulative indexes. Testing is listed by compound, species (strain), route of administration, and duration. Organizations and principal investigators are also indexed. Although emphasis is on current testing activities, retrospective test announcements are accepted for index entry and are used to enrich the Frawley Index made available by Jack Frawley of Hercules, Inc. Each month, all forms received during the previous month are reproduced in TOX-TIPS for distribution to toxicologists and other users and supporters of toxicological research.

PB-267 981/9GA **PC A03/MF A01**
Battelle Columbus Labs., Ohio.
Dietary Subacute Toxicity of Ethylene Thiourea in the Laboratory Rat.
Environmental health effects research series,
Ralph I. Freudenthal. May 77, 50p EPA/600/1-77/023
Contract EPA-68-02-1715
See also interim rept. dated Sep 76, PB-259 915.

Descriptors: *Fungicides, *Toxicity, *Thyroid gland, Rats, Laboratory animals, Pesticides, Degradation, Thyroid hormones, Malignant neoplasms, Pathology, Physiological effects, Thyroid hormones, Histology, Sublethal dosage, Ingestion(Biology), Toxic tolerances, Bioassay, Permissible dosage, Nitrogen organic compounds, Sulfur organic compounds.
Identifiers: Cancer, Histopathology, *Imidazolidine-thione, Triazole/amino, Thiouracil/propyl.

Ethylene thiourea (ETU) was fed to groups of rats at 0, 1, 5, 25, 125 or 625 ppm for up to 90 days. Other groups of rats received either propylthiouracil (PTU; 125 ppm) or amitrole (50 ppm) in their diets as positive controls. Only those rats which received ETU at 125 or 625 ppm and those ingesting PTU or amitrole demonstrated a measurable toxic response. This toxicity was reflected as an alteration in thyroid function and a significant change in thyroid morphology. Ingestion of 625 ppm ETU or 125 ppm PTU resulted in very substantial decreases in serum triiodothyronine (T-3) and thyroxine (T-4). Marked increases in serum thryroid stimulating hormone (TSH) levels were found in the 625 and 125 ppm ETU rats, the 125 PTU rats and the rats receiving amitrole, at each time point this hormone was measured. While a statistically significant increase in serum T-4 and degree of thyroid hyperplasia was observed for the rats ingesting 25 ppm ETU for 60 days, normal thyroid hormone levels and thyroid morphology was found in the rats on 25 ppm ETU for either 30 or 90 days. The no-effect level for dietary ETU in this 90-day study is considered to be 25 ppm, equivalent to an average intake ranging from 19.5 mg/kg body weight at week 1 to 12.5 mg/kg body weight at week 12.

PB-268 118/7GA **PC A02/MF A01**
Health Effects Research Lab., Research Triangle Park, N.C.
Biological Assessment of Continuous Exposure to Tritium and Lead in the Rat.
Journal article,
D. F. Cahill, L. W. Reiter, J. A. Santolucito, G. I. Rehnberg, and M. E. Ash. 1976, 15p EPA/600/J-76/063
Pub. in Biological and Environmental Effects of Low-Level Radiation, v2, International Atomic Energy Agency, Vienna, IAEA-SM-202/305, p65-78 1976.

Descriptors: *Lead, *Tritium, *Radiation effects, Radioactive isotopes, Potable water, Rats, Laboratory animals, Exposure, Life cycles, Reproduction(Biology), Central nervous system, Brain, Catecholamine, Dosage, Responses, Toxicology, Toxicity, Bioassay.
Identifiers: Reprints, Synergism, *Water pollution effects(Animals), Progeny.

In an attempt to contribute information on the effects of simultaneous exposure to two potentially synergistic environmental pollutants the authors have chronically administered tritiated water (HTO) and lead (Pb) to rats. HTO and Pb were selected because they are ubiquitous in the environment; technological advances have significantly increased their environmental levels; both are transplacentally transferred and can affect intrauterine development. Further, exposure to radiation or Pb in utero can produce postnatal neurological and reproductive dysfunction. The chronic exposure levels employed were 0.01 - 1.0 micro Ci HTO/ml body water (3-300 millirads/day) and 5 and 50 ppm of Pb in drinking water. These are, respectively, 2-200 times MPCw for an individual in the general population and 100-1000 times the U.S. Drinking Water Standards.

PB-268 139/3GA **PC A02/MF A01**
Health Effects Research Lab., Research Triangle Park, N.C.
Acid Precipitation: Effects of Sulfur Dioxide and Sulfate Aerosol Particles on Human Health.
Journal article,
David L. Coffin, and John H. Knelson. 1976, 5p EPA/600/J-76/067
Pub. in AMBIO, v5 n5-6 p249-252 1976.

Descriptors: *Toxicity, *Sulfur dioxide, *Sulfuric acid, *Sulfates, Inhalation, Laboratory animals, Experimental data, Cations, Oxidation, Lung, Histamines, Toxicology, Acidity, Precipitation(Chemistry), Gases, Guinea pigs, Respiratory diseases, Public health.
Identifiers: Animal models, Reprints, *Air pollution effects(Humans), Toxic substances, Environmental health, *Acid rain.

While human health impairment has been attributed to pollution by sulfur dioxide (SO2), data from inhalation studies in animals show that its oxidation products are more irritating. Population surveys in which suspended sulfate was a co-variant suggest that certain health parameters are associated more strongly with sulfate than with SO2. Recent work with biological models indicate that the sulfates and sulfuric acid act on the lung through the release of histamine and the degree of release is related to the specific cation present. Attention should be given to sulfates and specific cations in atmospheric monitoring.

September 16, 1977 97

FIGURE 4-7

NTIS Data Elements on SDC

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ANALYSES PREPARED BY FEDERAL AGENCIES OR THEIR CONTRACTORS AND GRANTEES.  FILE
COVERS 1970 TO DATE; IS UPDATED BIWEEKLY.  RATES ARE $45/HR & $.08/CIT.
--------------------------------------------------------------------------------
   SEARCH          ELEMENT NAME              PRINT          SEARCH
  QUALIFIER                                QUALIFIER       EXAMPLES
--------------------------------------------------------------------------------
    /BI          BASIC INDEX                  BI         MASS AND TRANSPORTATION
                 (INCLUDES SINGLE WORDS                  *ROCK AND *MECHANICS
                 FROM TITLES, INDEX TERMS,
                 SUPPLEMENTARY TERMS, &
                 MAJOR INDEX TERM WORDS
                 WITH ASTERISKS)
   IN BI         INDEX TERMS                  IT
   IN BI         SUPPLEMENTARY TERMS          ST
   IN BI         TITLE                        TI
--------------------------------------------------------------------------------

    /AN          ACCESSION NUMBER             AN         PB2396994SL/AN
    /AU          AUTHORS                      AU         MAYNE, A:/AU
    /OS          ORGANIZATIONAL SOURCE        OS         UNITED/OS AND NUCLEAR/OS
    /PY          PUBLICATION YEAR             PY         1 AND LESS THAN 77
    /IS          ISSUE                        IS         U7710/IS
    /SPO         SPONS. ORG. AC./NO.          SPO        DOT/SPO AND ALL AUTOMOB:
    /NU          NUMBERS                      NU         DOTHS3103595/NU
                   REPORT NUMBERS             RN
                   PROJECT NUMBERS            PN
                   TASK NUMBERS               TN
                   CONTRACT/GRANT NUMBERS     CG
    /CC          CATEGORY CODES               CC         92B/CC AND AERIAL
    /UP          UPDATE CODE                  —          7510/UP AND 20F/CC
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  STRS ONLY      TITLE ANNOTATI               TA
  STRS ONLY      TITLE NOTE                   TNO
  STRS ONLY      PAGINATION/DATE              PD
  STRS ONLY      NTIS PRICES                  PR
  STRS ONLY      AVAILABILITY                 AV
  STRS ONLY      NOTES                        NO
  STRS ONLY      ABSTRACT                     AB
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FIGURE 4-8

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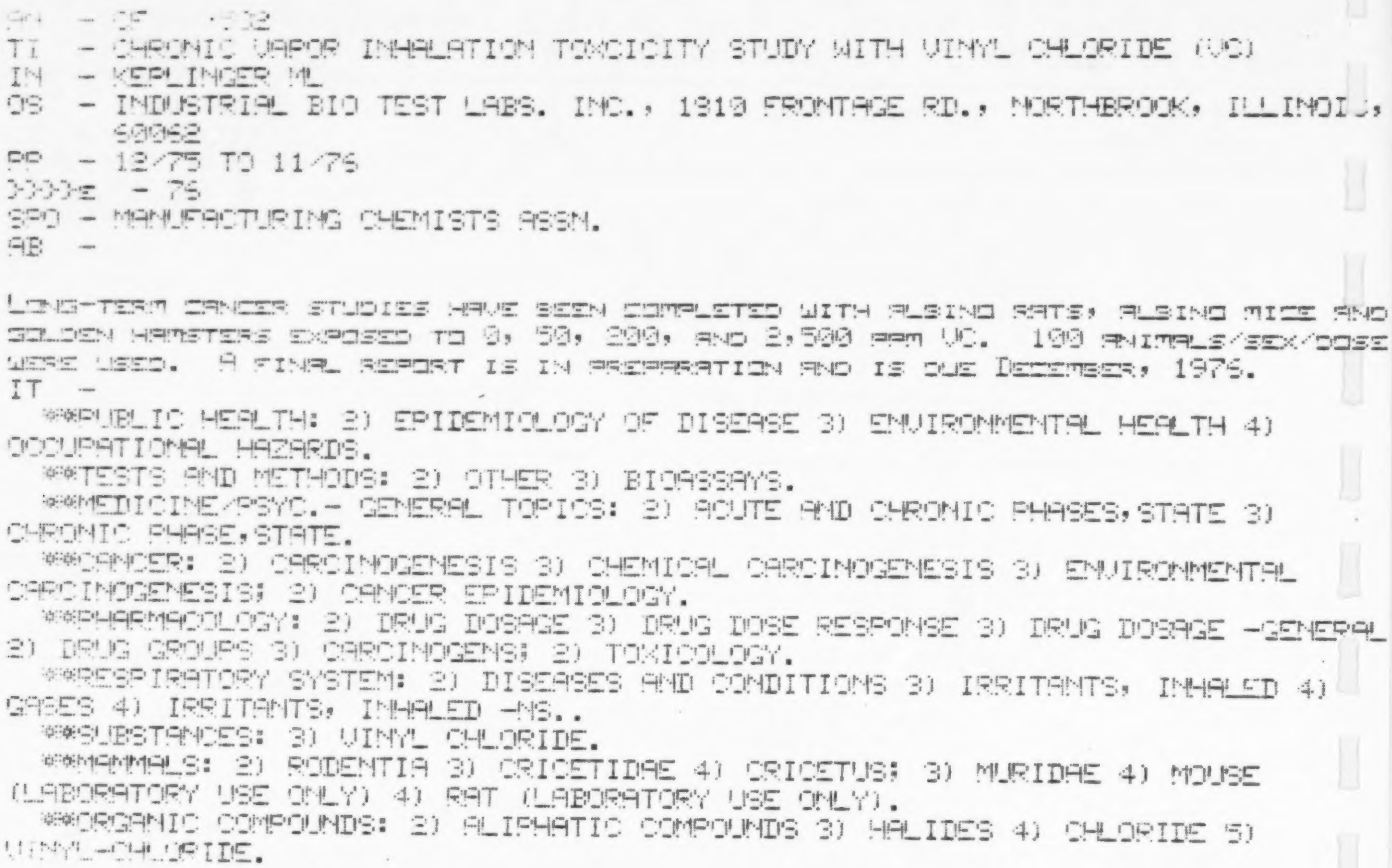

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AN  - CF    [illegible]2
TI  - CHRONIC VAPOR INHALATION TOXCICITY STUDY WITH VINYL CHLORIDE (VC)
IN  - KEPLINGER ML
OS  - INDUSTRIAL BIO TEST LABS. INC., 1810 FRONTAGE RD., NORTHBROOK, ILLINOI ,
      60062
PP  - 12/75 TO 11/76
>>>>E  - 76
SPO - MANUFACTURING CHEMISTS ASSN.
AB  -

LONG-TERM CANCER STUDIES HAVE BEEN COMPLETED WITH ALBINO RATS, ALBINO MICE AND
GOLDEN HAMSTERS EXPOSED TO 0, 50, 200, AND 2,500 PPM VC.  100 ANIMALS/SEX/DOSE
WERE USED.  A FINAL REPORT IS IN PREPARATION AND IS DUE DECEMBER, 1976.
IT  -
  **PUBLIC HEALTH: 2) EPIDEMIOLOGY OF DISEASE 3) ENVIRONMENTAL HEALTH 4)
OCCUPATIONAL HAZARDS.
  **TESTS AND METHODS: 2) OTHER 3) BIOASSAYS.
  **MEDICINE/PSYC.- GENERAL TOPICS: 2) ACUTE AND CHRONIC PHASES,STATE 3)
CHRONIC PHASE,STATE.
  **CANCER: 2) CARCINOGENESIS 3) CHEMICAL CARCINOGENESIS 3) ENVIRONMENTAL
CARCINOGENESIS; 2) CANCER EPIDEMIOLOGY.
  **PHARMACOLOGY: 2) DRUG DOSAGE 3) DRUG DOSE RESPONSE 3) DRUG DOSAGE -GENERAL
2) DRUG GROUPS 3) CARCINOGENS; 2) TOXICOLOGY.
  **RESPIRATORY SYSTEM: 2) DISEASES AND CONDITIONS 3) IRRITANTS, INHALED 4)
GASES 4) IRRITANTS, INHALED -NS..
  **SUBSTANCES: 3) VINYL CHLORIDE.
  **MAMMALS: 2) RODENTIA 3) CRICETIDAE 4) CRICETUS; 3) MURIDAE 4) MOUSE
(LABORATORY USE ONLY) 4) RAT (LABORATORY USE ONLY).
  **ORGANIC COMPOUNDS: 2) ALIPHATIC COMPOUNDS 3) HALIDES 4) CHLORIDE 5)
VINYL-CHLORIDE.
```

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Information about each project is supplied by the funding organization on a single-page Notice of Research Project (NRP). This NRP represents the basic output document of the SSIE system. An example of an NRP is illustrated in Figure 4-9. Each NRP records salient facts about a research project, including supporting organizations, grant or contract number, performing organization, principal investigator, coinvestigators, project title, period covered, funding, and a technical description of the project.

Words in the project title and technical description are matched with those in the SSIE classifying dictionary to form a subject index for each NRP. The NRP is further augmented with conceptual indexing which cannot be accomplished by a computer. This conceptual indexing is performed by SSIE staff scientists with expertise in a particular subject area. The same scientist responsible for the indexing in a particular field, is responsible for searching the data base in that field. Administrative index codes, such as investigator, location funding, etc., are also associated with a NRP to provide a comprehensive inverted search file.

The disc storage capacity of the computerized SSIE data base system limits the number of NRPs that can be accessed on-line. Therefore the active SSIE file only contains research projects that were reported in the last two fiscal years. A historical file of all NRPs that have been registered is maintained by SSIE off-line.

There are several search services provided by SSIE that would be relevant to the CTSS General Inquiry subsystem:

Custom Searches - Based on a user's request for information, SSIE staff scientists will search the active data base for NRPs that meet the specified search criteria. Searches can be specified combining any of the subject, conceptual, or administrative indexes into as a broad or as narrow criteria as desired. Contact between the user and the scientist conducting the search insures that the user needs are fully understood so that the search results are relevant and meaningful. The fee for this service is $60.00 for the search and the first 50 project notices retreived, plus $.25 for each additional NRP.

Research Information Packages

On a periodic basis, SSIE scientists conduct and review searches of the active data base for NRPs on subjects of current interest. The results of these searches are a series of research packages which are available at lower rates than comparable custom searches. The contents of the package are updated at least every 90 days. Some current research packages that are relevant are listed below:

- Effects of environmental radiation on man and animals
- Health hazards of particulate inhalation

- Health hazards of metals in the environment to man and animals
- Accidental DDT poisoning in man and mammals
- Toxic effects of lead and mercury in man and mammals
- Toxicity of gaseous halocarbons

The price for these packages varies according to the number of NRPs retrieved as follows: 1 to 24 NRPs-$35.00; 25 to 100 NRPs-$45.00; 101 to 200 NRPs-$55.00; 201 to 300 NRPs-$65.00; etc.

Selective Dissemination of Information (SDI)

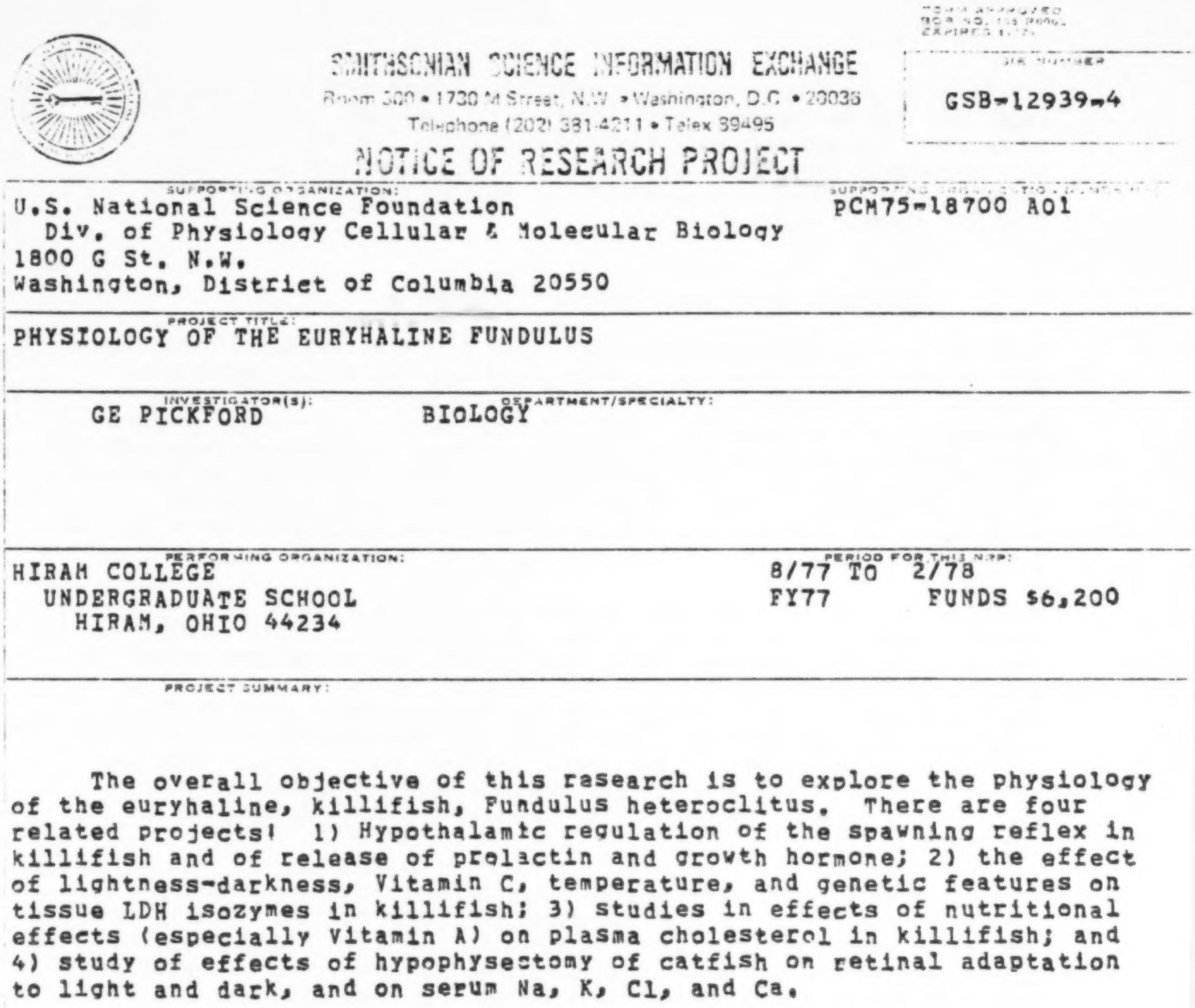
For users wishing to receive regular updates of custom searches or research information packages, SSIE offers two SDI services. Once a user interest profile is established, the active file is routinely searched according to the profile requirements to identify all new or newly updated NRPs added to the file since the last search. The Standard SDI Service provides twelve monthly search updates that are automatically generated by computer for a single fee of $180.00. These searches are not reviewed by scientists for relevance to user needs. If users desire a careful scientific review for each update, SSIE provides a Custom SDI Service that is performed on a quarterly basis. Staff scientists review both the search strategy and results of each search to assure maximum relevance to a specific profile. The quarterly costs for this service is $50.00 for the search and the first 50 project notices, plus $.25 for each additional NRP.

Custom Searches of Historical Files - Due to storage limitations, only a certain number of the most recently registered projects are available on-line. Projects registered prior to the cutoff data are stored off-line in an historical file. For users desiring the broadest possible coverage, SSIE will conduct searches of the historical file according to user-specified requirements. Subject and/or administrative indexes can be used in defining search strategies. Search results are reproduced in hard copy from microfilmed records, and are reviewed by staff scientists for relevance to user's requests. The fee for this service is $200.00 plus $.50 per NRP that is reproduced. This service usually takes 2 to 3 weeks to complete.

On-Line Search Service - The SSIE data base is available on-line through a national time-sharing network. This service enables users to search the file directly, instead of have an information specialist conduct the search and retrieve information based on user requirements. Currently, on-line access is available through the System Development Corporation Search Service, and is being planned for Lockheed's DIALOG Information System. Interaction with the data base is accomplished through an English-like search and retrieval language which is easy to understand and use, and which requires

FIGURE 4-9

Sample NRP From SSIE



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NOTICE OF RESEARCH PROJECT

SIE NUMBER:
GSB-12939-4

SUPPORTING ORGANIZATION:
U.S. National Science Foundation
Div. of Physiology Cellular & Molecular Biology
1800 G St. N.W.
Washington, District of Columbia 20550

PCM75-18700 A01

PROJECT TITLE:
PHYSIOLOGY OF THE EURYHALINE FUNDULUS

INVESTIGATOR(S): GE PICKFORD

DEPARTMENT/SPECIALTY: BIOLOGY

PERFORMING ORGANIZATION:
HIRAM COLLEGE
UNDERGRADUATE SCHOOL
HIRAM, OHIO 44234

PERIOD FOR THIS NRP:
8/77 TO 2/78
FY77 FUNDS $6,200

PROJECT SUMMARY:

The overall objective of this research is to explore the physiology of the euryhaline, killifish, Fundulus heteroclitus. There are four related projects! 1) Hypothalamic regulation of the spawning reflex in killifish and of release of prolactin and growth hormone; 2) the effect of lightness-darkness, Vitamin C, temperature, and genetic features on tissue LDH isozymes in killifish; 3) studies in effects of nutritional effects (especially Vitamin A) on plasma cholesterol in killifish; and 4) study of effects of hypophysectomy of catfish on retinal adaptation to light and dark, and on serum Na, K, Cl, and Ca.

little or no previous technical experience. Figure 4-10 lists the data items that can be searched, and Figure 4-11 illustrates a typical Notice of Research Project retrieved from the data base. The SDC data base covers NRPs registered from fiscal year 1974 to the present, and is updated monthly. SDC charges no subscription or minimum fee. The user charge is $110 per connect hour.

4.2.4 TOX-TIPS (Toxicology Testing in Progress)

TOX-TIPS is a monthly publication sponsored by the Toxicology Information Subcommittee of the DHEW Committee to Coordinate Toxicology and Related Programs and is produced by the Toxicology Information Program of the National Library of Medicine. TOX-TIPS represents a cooperative venture among industry, government, and academia to share knowledge of long-term toxicological testing. The publication is closely related to the functions of the Smithsonian Science Information Exchange. Since industry and academia do not ultimately submit research project information to SSIE, TOX-TIPS attempts to obtain this data for inclusion in SSIE.

Monthly, cooperating organizations complete forms describing current or recently completed testing activities. The forms are identical to the Notice of Research Projects (NRPs) used by SSIE, hence they are compatible with that system (Section 4.2.3). The NRPs are edited by the TOX-TIPS staff and summaries are enriched with CAS Registry Numbers and molecular structures when appropriate. Each NRP is supplemented with bibliographic references to the chemical substance(s) that are the subject of that test being described. (These references are obtained from various on-line MEDLARS data bases). Figure 4-12 illustrates a project description in TOX-TIPS.

Each issue of TOX-TIPS carries cumulative indices which are updated on a quarterly basis. The index of compounds lists the test substance by name, species (strain), route of administration and duration. Tests that have been completed and published cite the journal or other report in which test data can be found. Another index lists the organizations cited in TOX-TIPS and the investigators associated with the particular organization. Figure 4-13 illustrates the two indices.

All NRPs received by TOX-TIPS are forwarded to the SSIE for inclusion in that system. A subscription to TOX-TIPS costs $25 per year.

4.2.5 Toxicology Research Projects Directory

The Toxicology Research Projects Directory is a quarterly publication sponsored by the Toxicology Information Subcommittee of the DHEW Committee to Coordinate Toxicology and Related Programs. NLM's Toxicology Information

FIGURE 4-10

SSIE Data Elements on SDC

[illegible] ON-GOING AND RECENTLY COMPLETED RESEARCH SPONSORED BY GOVERNMENT+ [illegible], ASSOCIATIONS AND FOUNDATIONS, ETC. BASIC AND APPLIED RESEARCH IN ALL AREAS OF THE LIFE, PHYSICAL, SOCIAL, BEHAVIORAL, AND ENGINEERING SCIENCES ARE+ INCLUDED. FILE COVERS FY1974 TO DATE; IS UPDATED MONTHLY. RATES ARE $110/HR &

$.25/CIT.+

SEARCH QUALIFIER	ELEMENT NAME	PRINT QUALIFIER	SEARCH+ EXAMPLES+
/BI	BASIC INDEX (INCLUDES SINGLE WORDS FROM TITLES AND ABSTRACTS; ALSO MULTI-WORD INDEX TERMS)+	—	BIOFEEDBACK AND ALPHA+ SOLAR ENERGY CONVERSION+ SOLAR AND ENERGY+
/IT	INDEX TERMS	IT	NERVOU+ SYSTEM -VERTEBRATA+ MILK/IT AND BODY FLUIDS+
/ST	SUPPLEMENTARY TERMS (INCLUDES TITLES &+ ABSTRACTS, 50 WORDS TOTAL)+	ST	ADOPTION/ST+
/AN	ACCESSION NUMBER	AN	GPE0014390: /AN+
/IN (AU)	INVESTIGATORS	IN (AU)	JENKINS D#/AU+
/OS	ORGANIZATIONAL SOURCE	OS	CALIFORNIA/OS+
/CI	CITY	—	BERKELEY/CI+
/ST	STATE	—	FRANCE/SE+
/FY	FISCAL YEAR	FY	1 AND GREATER THAN 75+
/UP	UPDATE CODE	—	2 AND 7712/UP+
STRS ONLY	PERIOD OF PERFORMANCE	PP+	
STRS ONLY	SPONSORING ORGANIZATION	SPO+	
STRS ONLY	FUNDING	FUND+	
STRS ONLY	SPONS. ORG. CONT. NO.	CN+	

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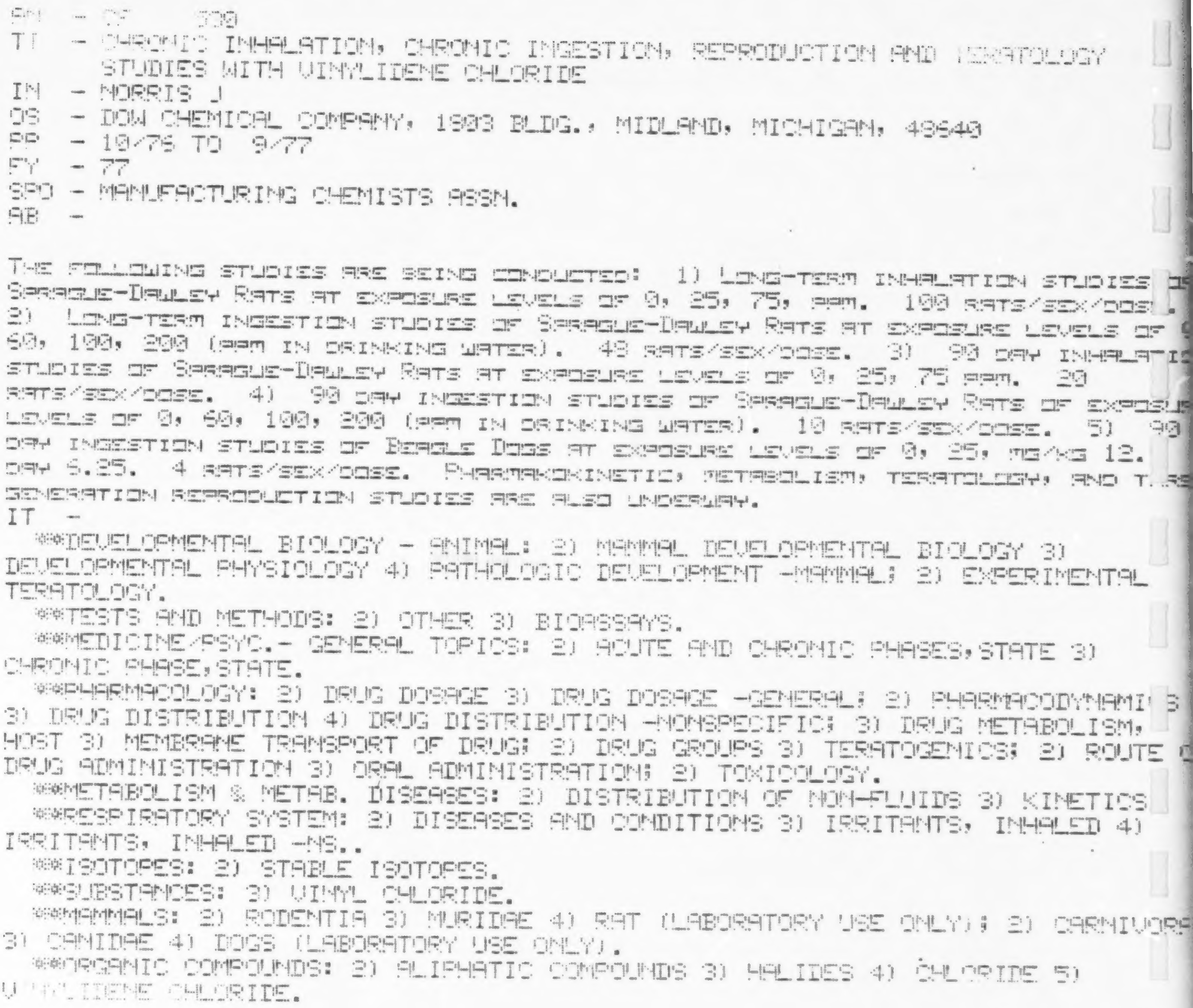
FIGURE 4-11

SSIE Citation From SDC



```
AN  - CF    300
TI  - CHRONIC INHALATION, CHRONIC INGESTION, REPRODUCTION AND TERATOLOGY
      STUDIES WITH VINYLIDENE CHLORIDE
IN  - NORRIS J
OS  - DOW CHEMICAL COMPANY, 1803 BLDG., MIDLAND, MICHIGAN, 48640
PP  - 10/76 TO  9/77
FY  - 77
SPO - MANUFACTURING CHEMISTS ASSN.
AB  -

THE FOLLOWING STUDIES ARE BEING CONDUCTED:  1) LONG-TERM INHALATION STUDIES
SPRAGUE-DAWLEY RATS AT EXPOSURE LEVELS OF 0, 25, 75, PPM.  100 RATS/SEX/DOS.
2)  LONG-TERM INGESTION STUDIES OF SPRAGUE-DAWLEY RATS AT EXPOSURE LEVELS OF
60, 100, 200 (PPM IN DRINKING WATER).  48 RATS/SEX/DOSE.  3)  90 DAY INHALATI
STUDIES OF SPRAGUE-DAWLEY RATS AT EXPOSURE LEVELS OF 0, 25, 75 PPM.  20
RATS/SEX/DOSE.  4)  90 DAY INGESTION STUDIES OF SPRAGUE-DAWLEY RATS OF EXPOSU
LEVELS OF 0, 60, 100, 200 (PPM IN DRINKING WATER).  10 RATS/SEX/DOSE.  5)  90
DAY INGESTION STUDIES OF BEAGLE DOGS AT EXPOSURE LEVELS OF 0, 25, MG/KG 12.
DAY 6.25.  4 RATS/SEX/DOSE.  PHARMAKOKINETIC, METABOLISM, TERATOLOGY, AND T..RE
GENERATION REPRODUCTION STUDIES ARE ALSO UNDERWAY.
IT  -
  **DEVELOPMENTAL BIOLOGY - ANIMAL: 2) MAMMAL DEVELOPMENTAL BIOLOGY 3)
DEVELOPMENTAL PHYSIOLOGY 4) PATHOLOGIC DEVELOPMENT -MAMMAL; 2) EXPERIMENTAL
TERATOLOGY.
  **TESTS AND METHODS: 2) OTHER 3) BIOASSAYS.
  **MEDICINE/PSYC.- GENERAL TOPICS: 2) ACUTE AND CHRONIC PHASES,STATE 3)
CHRONIC PHASE,STATE.
  **PHARMACOLOGY: 2) DRUG DOSAGE 3) DRUG DOSAGE -GENERAL; 2) PHARMACODYNAMICS
3) DRUG DISTRIBUTION 4) DRUG DISTRIBUTION -NONSPECIFIC; 3) DRUG METABOLISM,
HOST 3) MEMBRANE TRANSPORT OF DRUG; 2) DRUG GROUPS 3) TERATOGENICS; 2) ROUTE
DRUG ADMINISTRATION 3) ORAL ADMINISTRATION; 2) TOXICOLOGY.
  **METABOLISM & METAB. DISEASES: 2) DISTRIBUTION OF NON-FLUIDS 3) KINETICS
  **RESPIRATORY SYSTEM: 2) DISEASES AND CONDITIONS 3) IRRITANTS, INHALED 4)
IRRITANTS, INHALED -NS..
  **ISOTOPES: 2) STABLE ISOTOPES.
  **SUBSTANCES: 3) VINYL CHLORIDE.
  **MAMMALS: 2) RODENTIA 3) MURIDAE 4) RAT (LABORATORY USE ONLY); 2) CARNIVORA
3) CANIDAE 4) DOGS (LABORATORY USE ONLY).
  **ORGANIC COMPOUNDS: 2) ALIPHATIC COMPOUNDS 3) HALIDES 4) CHLORIDE 5)
VINYLIDENE CHLORIDE.
```

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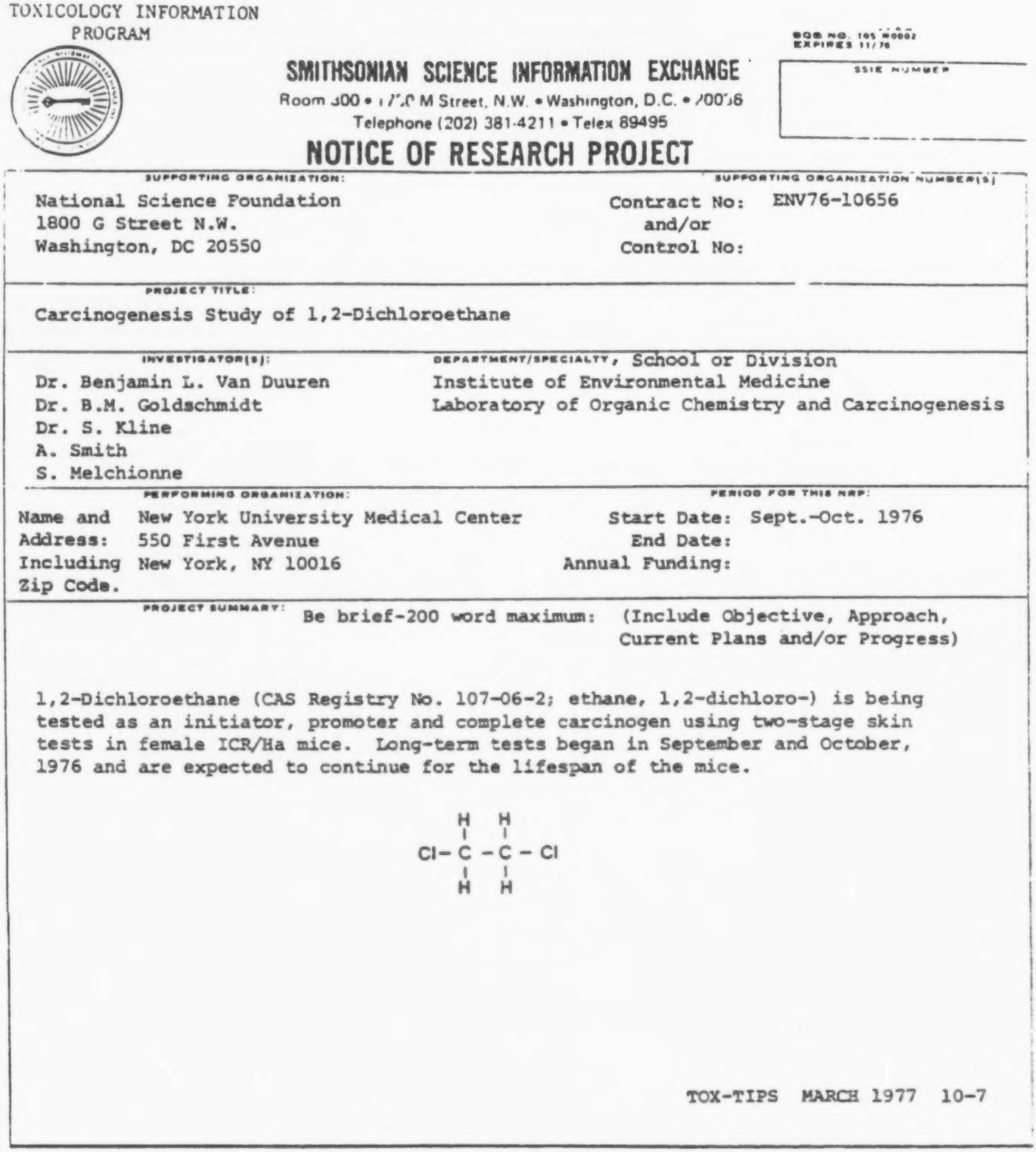
FIGURE 4-12 (1)

TOX-TIPS Project Description



TOXICOLOGY INFORMATION
PROGRAM

BOB NO. 105 R0002
EXPIRES 11/76

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
Room 300 • 1730 M Street, N.W. • Washington, D.C. • 20036
Telephone (202) 381-4211 • Telex 89495

SSIE NUMBER

NOTICE OF RESEARCH PROJECT

SUPPORTING ORGANIZATION:
National Science Foundation
1800 G Street N.W.
Washington, DC 20550

SUPPORTING ORGANIZATION NUMBER(S)
Contract No: ENV76-10656
and/or
Control No:

PROJECT TITLE:
Carcinogenesis Study of 1,2-Dichloroethane

INVESTIGATOR(S):
Dr. Benjamin L. Van Duuren
Dr. B.M. Goldschmidt
Dr. S. Kline
A. Smith
S. Melchionne

DEPARTMENT/SPECIALTY, School or Division
Institute of Environmental Medicine
Laboratory of Organic Chemistry and Carcinogenesis

PERFORMING ORGANIZATION:
Name and Address: Including Zip Code. New York University Medical Center
550 First Avenue
New York, NY 10016

PERIOD FOR THIS NRP:
Start Date: Sept.-Oct. 1976
End Date:
Annual Funding:

PROJECT SUMMARY: Be brief-200 word maximum: (Include Objective, Approach, Current Plans and/or Progress)

1,2-Dichloroethane (CAS Registry No. 107-06-2; ethane, 1,2-dichloro-) is being tested as an initiator, promoter and complete carcinogen using two-stage skin tests in female ICR/Ha mice. Long-term tests began in September and October, 1976 and are expected to continue for the lifespan of the mice.

$$\begin{array}{ccccccc} & & H & & H & & \\ & & | & & | & & \\ Cl & - & C & - & C & - & Cl \\ & & | & & | & & \\ & & H & & H & & \end{array}$$

TOX-TIPS MARCH 1977 10-7

FIGURE 4-12 (2)

TOX-TIPS Project Description

The bibliographic references (author, title, source) on this page have been obtained from searches of the following National Library of Medicine's on-line retrieval files: TOXLINE, CHEMLINE, MEDLINE, SDILINE, and CANCERLINE. The searches, made on the substances that are the subject of the test described in the Notice of Research Project, usually have retrieved the most recent citations from these files. Because these searches have not been exhaustive, the investigator may wish to obtain more complete searches on the test substances by searching the NLM on-line files or by contacting the Toxicology Information Response Center (TIRC) at the Oak Ridge National Laboratory, P.O. Box X, Building 7509, Oak Ridge, TN 37830 — Phone: 615-483-8611, extension 31433.

Ames BN ; McCann J
CARCINOGENS ARE MUTAGENS: A SIMPLE TEST SYSTEM.
In: Screening Tests in Chemical Carcinogenesis; Edited by R. Montesano; H. Bartsch; L. Tomatis; W. Davis. International Agency for Res. on Cancer. (Brussels, 9-12 June 1975): no. 12, pp. 493-501, 503-504; 1976

Horvath AL
Maximum permissible concentrations of halogenated hydrocarbons in reservoir waters_a review.
Chem. Ind. (London) 1: 26-27; 1976.(46 references)

Kokarovtseva MG ; Larionov VG ; Zorina VA
[Effect of dichloroethane on the activity of certain enzyme systems of the blood and indices of its morphological composition in warm-blooded animals]
Vrach Delo (5):126-9, 1976

McCann J ; Simmon V ; Streitwieser D ; Ames BN
MUTAGENICITY OF CHLOROACETALDEHYDE, A POSSIBLE METABOLIC PRODUCT OF 1,2-DICHLOROETHANE (ETHYLENE DICHLORIDE), CHLOROETHANOL (ETHYLENE CHLOROHYDRIN), VINYL CHLORIDE AND CYCLOPHOSPHAMIDE
Proc Natl Acad Sci USA; 72(8):3190-3193 1975

Rannug U ; Ramel C
THE MUTAGENICITY OF WASTE PRODUCTS FROM THE VINYL CHLORIDE INDUSTRIES [MEETING ABSTRACT].
Mutat Res; 38(2):113 1976

Zhizhonkov NV
[Acute dichloroethane poisoning]
Vrach Delo (6):127-8, Jun 76

FIGURE 4-13 (1)

TOX-TIPS Index by Compound

- Butylated hydroxytoluene
  - Rat - oral - 2-year...Joint FAO/WHO Expert Committee on Food Additives --Ninth Report. Specifications for the Identity and Purity of Food Additives and Their Toxicological Evaluation: Some Antimicrobials, Antioxidants, Emulsifiers, Stabilizers, Flour-Treatment Agents, Acids and Bases. Tech. Rep. Ser. Wld. Hlth. Org. 339 (1966)
- Butylbenzylphthalate
  - Mouse - diet - 2-year... 6:35
  - Rat - diet - 2-year... 6:35
- Butyl-3,4-dihydro-2,2-dimethyl-4-oxo-1-2H-pyran-6-carboxylate, see Indalone
- 1,3-Butylene glycol
  - Rat - oral - 2-year...Toxicol. Appl. Pharmacol. 5, 358 (1964)
- Butylene glycol adipic acid polyester, see Santicizer 334F
- 2-(para-tert-Buytlphenoxy) isopropyl 2'-chloroethyl sulfite, see Aramite
- 4-tert-Butylphenyl salicylate
  - Rat - oral - 2-year...J. Agr. Food Chem. 11(6), 468 (1963)
- Butyl stearate
  - Rat - oral - 2-year...AMA Arch. Ind. Hyg. Occup. Med. 7, 310 (1953)
- Cadmium and zinc
  - Rat - feed - 15-month... 9:41
- Cadmium chloride
  - Rat - oral - 2-year...Chemicals in Foods: A Report to the Food and Drug Officials on Current Developments, Part II. Pesticides 16(2), 47 (1952)
- Calcium disodium ethylenediaminetetraacetate
  - Rat - oral - 2-year...Toxicol. Appl. Pharmacol. 5(2), 142 (1963)
- Calcium fluoride
  - Guinea pig - inhalation - 4-month...10:41
- Calcium sulfate, particulate
  - Guinea pig - inhalation - 60-day... 9:17
  - Rat - inhalation - 60-day... 9:17
- Caprolactam
  - Mouse - diet - 2-year... 5:25
  - Rat - diet - 2-year... 5:25
- Captan
  - Rat - oral - 2-year...Summaries of Pesticide Toxicity. Association of Food and Drug Officials of the U.S., Topeka, Kan. (1965)

TOX-TIPS MARCH 1977 10-47

FIGURE 4-13 (2)

TOX-TIPS Index by Organization

- Food and Drug Research Laboratories, Inc.
  - Bailey, David F.... 9:35
  - Gallo, Michael A.... 8:25
- Gulf South Research Institute
  - Wheeler, Ralph... 6:7, 6:9, 6:11, 6:13, 6:15, 6:17, 8:49, 8:51
- Hair Color Industry
  - Sponsored Studies... 5:11, 5:13, 5:15
- Industrial Bio-Test Laboratories
  - Goode, John... 3:8, 3:9
  - Keplinger, M.L.... 5:3, 5:5, 9:33
  - Kinoshita, Florence... 9:41
  - Lindberg, Dennis... 7:3, 7:5, 7:7, 7:9, 7:11, 7:13, 7:15, 7:17, 7:19, 7:21
- Institute for Medical Research and Occupational Health (Yugoslavia)
  - Kostial, Krista...10:39
- International Research & Development Corp.
  - Goldenthal, E.... 5:13, 5:15
- IIT Research Institute
  - Henry, M.... 7:49, 9:3
- Litton Bionetics Inc.
  - Beliles, Robert... 8:39, 8:47, 10:31
  - Brusick, David J....10:31
  - Garner, F.M.... 5:17, 5:19, 5:21, 5:23, 5:25, 5:27, 5:29, 5:31, 5:33
  - Hart, E. Ross...10:31
  - Manus, Alan G...10:31
  - Matheson, Dales W...10:31
  - Seibold, Herman R...10:31
- Lovelace Foundation for Medical Education and Research
  - Mokler, Brian V.... 3:2
  - Henderson, Thomas R.... 3:2
  - Damon, Edward G.... 3:2
  - Inhalation Toxicology Research Institute... 8:23
- Manufacturing Chemists Association
  - Sponsored Studies... 5:3, 5:5, 5:7, 5:9, 8:29, 8:31, 8:33, 8:35, 8:37, 8:39, 8:41, 8:43, 8:45, 8:47
- Mason Research Institute
  - Landon, John C. (Acting)... 6:19, 6:21, 6:23, 6:25, 6:27, 6:29, 6:31, 6:33, 6:35

TOX-TIPS MARCH 1977 10-84

Program supervises the project. The directory is an inventory of current research projects in toxicology and related fields selected from the Smithsonian Science Information Exchange data base. The emphasis of this directory is the manifestations of the exposure of man and animals to toxic substances.

Each issue provides information about relevant research projects registered with SSIE during the three-month period preceeding that issue. Approximately 2,500 project summaries are included in each issue.

The directory includes descriptions of research projects containing the same information found in the NRPs utilized by SSIE, followed by five sets of indices. Each project has an abstract which lists the project number, title of the project, principal investigators, the name and address of the laboratory conducting the test, the supporting organization, and funding information. Figure 4-14 illustrates a portion of the project description section.

There are several indexes in the directory. The Subject Index is based on the classification system developed by SSIE. Each Subject Index term is followed by a set of project titles and identifying project numbers. The index identifies specific chemical substances by name which would be most useful for CTSS users. Figure 4-15 illustrates a portion of the Subject Index. The directory also provides an Investigator Index, Performing Organization Index, Supporting Agency Index, and a Master Grant Number Index.

The directory is available from NTIS through publication No. NTISSUB/B/021. Single issues cost $15. A yearly subscription for a complete volume costs $50.

4.2.6 Evaluation and Recommendations

Table 4-1 presents a summary of the analysis of the data content requirements of the CTSS directory that are provided by the five existing information sources.

All of the existing information sources identify the chemical substance being tested by a common name or a preferred chemical name (i.e., CAS preferred name). Only MEDLARS and TOX-TIPS make use of the associated CAS Registry Number as an alternate means of identifying a chemical substance. However, the CAS Registry Numbers specified in these two data bases only cover a portion of the experiments that are cited. Since an integral part of the CSIN includes the use of CAS Registry Numbers as a common chemical substance identifier among data bases, it is recommended that an effort be made to include these numbers in information sources whenever possible.

FIGURE 4-14

Toxicology Research Projects Directory Citation

3. PHYSICAL AGENTS AND GASES

A no-effect level will be determined. The parameters to be measured will include: mortality rates; mean survival time, wet-dry weight ratio of lung tissue, and pathology. Other measurements of host defense alterations will include humoral and cell-mediated immunity response, phagocytic and bactericidal activity of lung defense cells.

SUPPORTED BY U.S. Environ. Protection Agy., Office of
Research & Dev.
funds n.a.

2.3.0017, RETENTION OF AEROSOLS IN LABORATORY ANIMALS

J.O. HUTCHIENS, Univ. of Chicago, School of Medicine, *Chicago, Illinois* 60637 (ES 00855-03)

The purpose of this project is to establish the locus and extent of retention of aerosol particles in the respiratory tracts of laboratory animals. Sub-gross anatomies of the respiratory tracts are being investigated with the aid of casts. Calculations are made regarding deposition of aerosols by impaction, settling and diffusion. Direct measurements of retention will be made by analysis of inhaled and exhaled air. Retentions are also estimated indirectly from toxicological effects of exposure to aerosols of various substances. The ultimate aim is to be able to interpret a given aerosol exposure for a laboratory animal in terms of effects to be expected in man.

SUPPORTED BY U.S. Dept. of Hlth. Ed. & Wel., National
Institutes of Health, Natl. Inst. of Env.
Hlth. Sci.
$46,252

2.3.0018, CHRONIC VAPOR INHALATION TOXCICITY STUDY WITH VINYL CHLORIDE (VC)

M.L. KEPLINGER, Industrial Bio Test Labs. Inc., *Northbrook, Illinois* 60062

Long-term cancer studies have been completed with albino rats, albino mice and golden hamsters exposed to 0, 50, 200, and 2,500 ppm VC. 100 animals/sex/dose were used. A final report is in preparation and is due December, 1976.

SUPPORTED BY Manufacturing Chem. Assn. Inc. - Wash.
D.C
funds n.a.

2.3.0019, STUDY ON THE EFFECTS FROM REPEATED INHALATION OF TRICHLOROETHYLENE VAPOR IN RATS AND MICE

M.L. KEPLINGER, Industrial Bio Test Labs. Inc., *Northbrook, Illinois* 60062

The following studies are in progress; 1. A two-year cancer study in Charles River rats exposed to 0, 100, 300, and 600 ppm. 120 rats/sex/exposure level. 2. A long-term cancer study in B6C3F1 mice exposed to 0, 100, 300, and 600 ppm. 130 mice/sex/exposure level.

SUPPORTED BY Manufacturing Chem. Assn. Inc. - Wash.
D.C
funds n.a.

2.3.0020, DISULFIRAM-OXYGEN THERAPY - OXYGEN TOXICITY CONCEPTS

M.D. FAIMAN, Univ. of Kansas, School of Pharmacy, *Lawrence, Kansas* 66044 (NS 07797-05A1)

We propose to investigate the relationship between the components of the GSH system in blood, lung, and brain of the intact animals with the onset of oxygen toxicity and the protection from this toxicity by disulfiram.

Specifically, we propose to investigate in detail the distribution and elimination of disulfiram, diethyldithiocarbamate, and their metabolites in blood in both mice and mongrel dogs and in lung and brain of mice, and to correlate the concentration of these drug species in blood and tissue with the oxygen protective action of disulfiram. We also propose to study in detail the effect of both hyperbaric oxygen and disulfiram on GSH, GSSG pyridine nucleotides (NAD, NADH, NADP, NADPH2), GSH peroxidase and GSH reductase in blood, lung and brain of mice. The effect of OHP and disulfiram on lipid peroxidation in blood, lung, and brain in mice also will be investigated.

A postulated mechanism for oxygen toxicity and the protective effects of disulfiram are presented. In these studies, disulfiram is being used as a tool to investigate the proposed relationship of the GSH system with oxygen toxicity.

SUPPORTED BY U.S. Dept. of Hlth. Ed. & Wel., National
Institutes of Health, Natl. Inst. Neuro. &
Com. Dis.
$38,616

2.3.0021, CONTROL OF AIR CONTAMINANTS IN THE HOME

P.J. ANNIS, Kansas State University, Agric. Experiment Station, *Manhattan, Kansas* 66502 (0004469)

OBJECTIVE: Determine the effects of hood geometry, hood-range relationship, and hood air flow rate upon airborne contaminant capture efficiency. Determine whether: Vacuum cleaning causes appreciable amount of settled dust to go into suspension, this dust differs in size and character from that normally in suspension, this dust behaves as normal atmospheric dust while in suspension, vacuum cleaner design has an effect upon these variables.

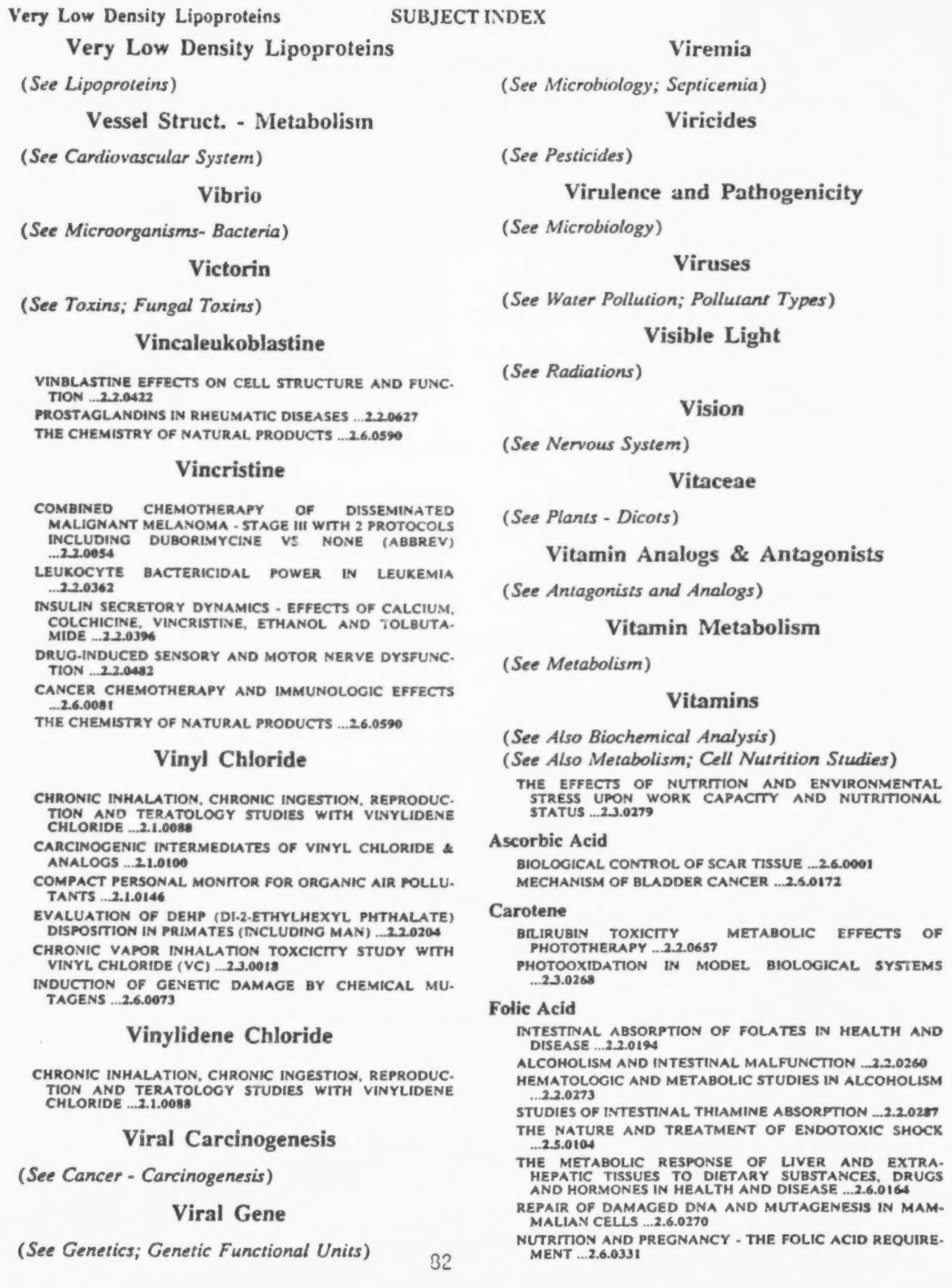
APPROACH: Using mock-up hoods, geometry, location and air flow will be varied and each combination tested for efficiency in solid aerosol and water vapor removal. Atmospheric dust in several homes will be sampled to ascertain the problems in determining dust concentration level. Periods immediately before and after vacuuming and while using several styles of vacuum cleaners will be studied. Samples would be taken on MSA 1106 BH glass-fiber paper using a Gelman No 13200 carbon-ring, pistontype portable vacuum pump. Later, samples would be taken on type AA Milipore filters, from which size analyses can be determined by the MSA-Whitby method.

PROGRESS: Subproject I: New Concepts in Cooking Contaminant Control. Using the artificial sciling specified for self-cleaning ovens in AHAM standard ER-3, additional ovens were tested for the amount of smoke emitted during their cleaning cyles and its effects upon smoke eliminator efficiency. Noting that some ranges had high surface temperatures, an AHAM standard probe was built & 35 ranges subjected to intensive analysis. Findings indicate at least one-third exceed maximum allowable surface temperatures under industry codes. Using previously obtained data, an attempt is also underway to optimize kitchen range hood air flow to achieve maximum energy conservation. Subproject II: The Effect of Vacuum Cleaning Upon Household Atmospheric Dust. Modification of an Electrolux vacuum cleaner air filtration system to achieve higher filtration efficiency was completed. The new unit used less efficient collection bag, & cleaning tests proved successful. The unit will be of great value to persons high efficiency pleated glass fiber cartridge at the exhaust fitting. If rug cleaning tests prove successful, the unit will be of great value to persons suffering from household dust allergy. (Text Abridged.)

SUPPORTED BY Kansas State Government - Topeka
funds n.a.

FIGURE 4-15

Toxicology Research Projects Directory Index



Very Low Density Lipoproteins SUBJECT INDEX

Very Low Density Lipoproteins

(*See Lipoproteins*)

Vessel Struct. - Metabolism

(*See Cardiovascular System*)

Vibrio

(*See Microorganisms- Bacteria*)

Victorin

(*See Toxins; Fungal Toxins*)

Vincaleukoblastine

VINBLASTINE EFFECTS ON CELL STRUCTURE AND FUNCTION ...2.2.0422
PROSTAGLANDINS IN RHEUMATIC DISEASES ...2.2.0627
THE CHEMISTRY OF NATURAL PRODUCTS ...2.6.0590

Vincristine

COMBINED CHEMOTHERAPY OF DISSEMINATED MALIGNANT MELANOMA - STAGE III WITH 2 PROTOCOLS INCLUDING DUBORIMYCINE VS NONE (ABBREV) ...2.2.0054
LEUKOCYTE BACTERICIDAL POWER IN LEUKEMIA ...2.2.0362
INSULIN SECRETORY DYNAMICS - EFFECTS OF CALCIUM, COLCHICINE, VINCRISTINE, ETHANOL AND TOLBUTAMIDE ...2.2.0396
DRUG-INDUCED SENSORY AND MOTOR NERVE DYSFUNCTION ...2.2.0482
CANCER CHEMOTHERAPY AND IMMUNOLOGIC EFFECTS ...2.6.0081
THE CHEMISTRY OF NATURAL PRODUCTS ...2.6.0590

Vinyl Chloride

CHRONIC INHALATION, CHRONIC INGESTION, REPRODUCTION AND TERATOLOGY STUDIES WITH VINYLIDENE CHLORIDE ...2.1.0088
CARCINOGENIC INTERMEDIATES OF VINYL CHLORIDE & ANALOGS ...2.1.0100
COMPACT PERSONAL MONITOR FOR ORGANIC AIR POLLUTANTS ...2.1.0146
EVALUATION OF DEHP (DI-2-ETHYLHEXYL PHTHALATE) DISPOSITION IN PRIMATES (INCLUDING MAN) ...2.2.0204
CHRONIC VAPOR INHALATION TOXCICITY STUDY WITH VINYL CHLORIDE (VC) ...2.3.0018
INDUCTION OF GENETIC DAMAGE BY CHEMICAL MUTAGENS ...2.6.0073

Vinylidene Chloride

CHRONIC INHALATION, CHRONIC INGESTION, REPRODUCTION AND TERATOLOGY STUDIES WITH VINYLIDENE CHLORIDE ...2.1.0088

Viral Carcinogenesis

(*See Cancer - Carcinogenesis*)

Viral Gene

(*See Genetics; Genetic Functional Units*)

Viremia

(*See Microbiology; Septicemia*)

Viricides

(*See Pesticides*)

Virulence and Pathogenicity

(*See Microbiology*)

Viruses

(*See Water Pollution; Pollutant Types*)

Visible Light

(*See Radiations*)

Vision

(*See Nervous System*)

Vitaceae

(*See Plants - Dicots*)

Vitamin Analogs & Antagonists

(*See Antagonists and Analogs*)

Vitamin Metabolism

(*See Metabolism*)

Vitamins

(*See Also Biochemical Analysis*)
(*See Also Metabolism; Cell Nutrition Studies*)

THE EFFECTS OF NUTRITION AND ENVIRONMENTAL STRESS UPON WORK CAPACITY AND NUTRITIONAL STATUS ...2.3.0279

Ascorbic Acid

BIOLOGICAL CONTROL OF SCAR TISSUE ...2.6.0001
MECHANISM OF BLADDER CANCER ...2.6.0172

Carotene

BILIRUBIN TOXICITY METABOLIC EFFECTS OF PHOTOTHERAPY ...2.2.0657
PHOTOOXIDATION IN MODEL BIOLOGICAL SYSTEMS ...2.3.0268

Folic Acid

INTESTINAL ABSORPTION OF FOLATES IN HEALTH AND DISEASE ...2.2.0194
ALCOHOLISM AND INTESTINAL MALFUNCTION ...2.2.0260
HEMATOLOGIC AND METABOLIC STUDIES IN ALCOHOLISM ...2.2.0273
STUDIES OF INTESTINAL THIAMINE ABSORPTION ...2.2.0287
THE NATURE AND TREATMENT OF ENDOTOXIC SHOCK ...2.5.0104
THE METABOLIC RESPONSE OF LIVER AND EXTRA-HEPATIC TISSUES TO DIETARY SUBSTANCES, DRUGS AND HORMONES IN HEALTH AND DISEASE ...2.6.0164
REPAIR OF DAMAGED DNA AND MUTAGENESIS IN MAMMALIAN CELLS ...2.6.0270
NUTRITION AND PREGNANCY - THE FOLIC ACID REQUIREMENT ...2.6.0331

TABLE 4-1

CTSS Directory Data Requirements

provided by

Existing Information Sources

Source Data Requirement	MEDLARS Bibliographic Reference System	National Technical Information Service	Smithsonian Science Information Exchange	TOX-TIPS	Toxicology Research Projects Directory
Test Substance Name	Yes	Yes	Yes	Yes	Yes
CAS Registry Number	Part.	No	No	Part.	No
Organization Conducting Test	Yes	Yes	Yes	Yes	Yes
Principal Person(s) Responsible for Test	Part.	Yes	Yes	Yes	Yes
Type of Test	Yes	Yes	Yes	Yes	Yes
Species	Yes	Yes	Yes	Yes	Yes
Route of Administration	Yes	Yes	Yes	Yes	Yes
Start and End Dates	Part.	Part.	Yes	Yes	Yes
Status of Experiment	Yes	Yes	Yes	Yes	Yes
Location of Detailed Test Data	No	No	No	No	No
IRLG-GLP Guidelines Followed	No	No	No	No	No
Published Test Results	Yes	Yes	No	No	No

Yes - Fully Supported
Part. - Partially Supported
No - Not Supported

None of the existing information sources indicates the location of detailed test data relating to a particular test. As stated in the data elements portion of the proposed CTSS, ideally the CTSS would cite all sources in addition to the laboratory that actually conducted the test where summary reports and/or detailed test data be obtained.

Because the IRLG-GLP testing guidelines have not yet been completed, no current research projects can use these guidelines. However, when these guidelines are implemented, that data element would be employed in the record. It should be noted that the TDMS already employs GLP screens in conducting their tests.

An analysis and evaluation of the test results by the original investigators or laboratory conducting the experiment is included in the information sources citing published animal test results: i.e., MEDLARS and NTIS. The other information sources, SSIE, TOX-TIPS, and the Toxicology Research Projects Directory, cite research projects in progress and therefore do not present test results.

None of the existing information sources references unpublished test results. Including experiments undertaken in support of product registration or otherwise financed without government support. Section 8(d) of the Toxic Substances Control Act (TSCA) provides EPA with the authority to request most such information requiring persons who manufacture, process, or distribute in commerce chemical substances or mixtures to maintain lists of health and safety studies conducted by them or for them and make these lists available to the Administrator. The Administrator is authorized to request the submission of any study appearing on the list. The capability to record and access these lists is currently being incorporated into the TSCA Chemical Data System[1], another core component of the CSIN being developed by OTS.

Based on the evaluation of existing capabilities to support user requirements, there is no need to develop additional information sources. Mechanisms and procedures currently exist to record and access information on-line pertaining to completed tests and current research. What is needed first is a concentrated effort to obtain all pertinent information on testing and research efforts. For instance, activities such as the TOX-TIPS program which obtain industrial research data should be expanded and encouraged. A corresponding effort should be made to inform the various CTSS users of these existing capabilities and of their potential uses.

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[1] TSCA Chemical Data System - also known as Chemicals in Commerce Information System. As presently conveived (CICIS Statement of Informational Decision-Making and Data Requirements, Draft Report, Informatics, Inc. July 1, 1978), CICIS will support information collected under TSCA authority, including for example toxicity testing of chemicals, and premanufacture notification.

Figure 4-16 illustrates the informational sources that could be utilized depending on the type of information desired and the access capability available to the CTSS user.

With respect to data access, MEDLARS, NTIS, and SSIE are all available on time-sharing networks. For users not having terminals, NTIS index and abstracts, TOX-TIPS, and the Toxicology Research Projects Directory are available by subscription in hard copy. While there is no one source which satisfies user needs as long as users are aware of the different sources and how to access each, no additional systems need be developed.

Not all these sources are available on the same network; access to each of them would require more than one "phone call." Mechanisms which would assist the user in searching these data bases would include use of CAS Registry Numbers, registration in the Chemical Data Bases Directory, and referencing in the Chemical Structure and Nomenclature System. (See Section 4.4 for a detailed discussion of these systems).

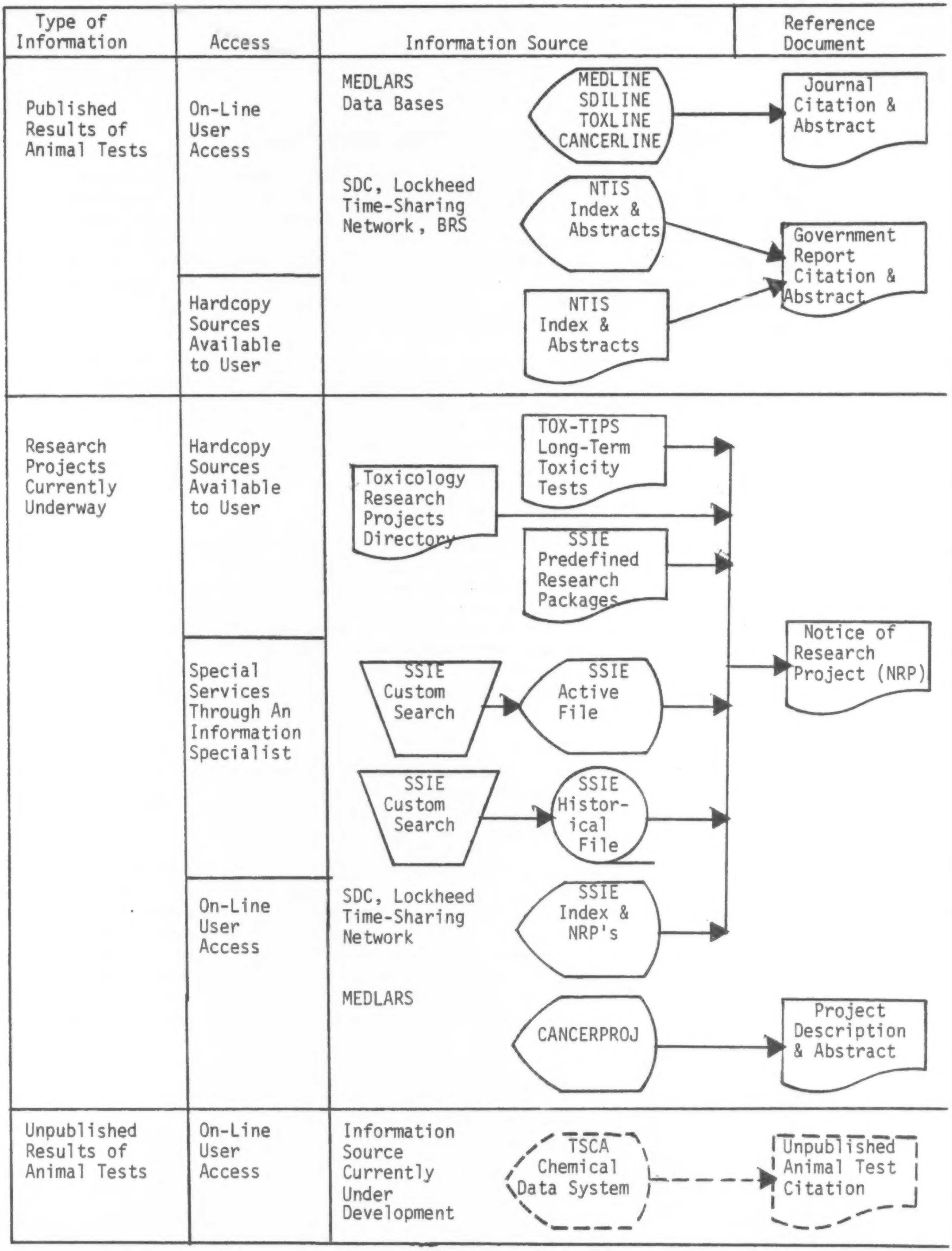
4.3 Data Acquisition and Analysis

The idealized design of the Data Collection, Data Submission, Storage and Conversion, and Detailed Analysis and Evaluation subsystems represents a comprehensive, integrated system to define, gather, and review test data. Since the requirements for these subsystems are interdependent, they are each discussed in this section. Sigma Data surveyed several existing systems to determine if components of them could be incorporated into the CTSS, or if components could be enhanced to meet CTSS requirements. These existing systems include:

- Medical classification and nomenclature Systems-users indicated that the greatest need for standardization was in the greatest need for standardization was in the area of recording animal observations (physical and behavioral) during treatment, and noting pathology findings (gross and microscopic) at death.
- Laboratory Animal Data Bank - a joint effort by the National Library of Medicine and Battelle Columbus Laboratories to collect data on Laboratory animals used as experimental controls at laboratories from diverse organizations, including government, industrial and independent labs. This data is available on-line for analysis and evaluation.
- Toxicology Data Management System - a joint effort by the National Center for Toxicological Research and the National Cancer Institute to develop an integrated system that employs automated data collection and reporting techniques spanning all aspects of laboratory testing, from test substance selection to final report preparation. Many of the capabilities designed for the TDMS are identical to those proposed for the CTSS.

FIGURE 4-16

Information Sources Included In The CTSS General Inquiry Subsystem


Type of Information
Access
Information Source
Reference Document
Published Results of Animal Tests
On-Line User Access
MEDLARS Data Bases
MEDLINE
SDILINE
TOXLINE
CANCERLINE
Journal Citation & Abstract
SDC, Lockheed Time-Sharing Network, BRS
NTIS Index & Abstracts
Government Report Citation & Abstract
Hardcopy Sources Available to User
NTIS Index & Abstracts
Research Projects Currently Underway
Hardcopy Sources Available to User
TOX-TIPS Long-Term Toxicity Tests
Toxicology Research Projects Directory
SSIE Predefined Research Packages
Notice of Research Project (NRP)
Special Services Through An Information Specialist
SSIE Custom Search
SSIE Active File
SSIE Custom Search
SSIE Histor-ical File
On-Line User Access
SDC, Lockheed Time-Sharing Network
SSIE Index & NRP's
MEDLARS
CANCERPROJ
Project Description & Abstract
Unpublished Results of Animal Tests
On-Line User Access
Information Source Currently Under Development
TSCA Chemical Data System
Unpublished Animal Test Citation

4.3.1 Medical Classification and Nomenclature Systems

One of the earliest systems, the International Classification of Diseases (ICD), was developed in 1890 to provide a list of categories for compiling mortality statistics. ICD is a classification system rather than a nomenclature system in that not every condition is classified in a separate code number, but there is a category or grouping into which known diagnoses or symptoms can be placed. A retrieval uses the same narrow and broad groupings used in the coding process. Except for the most general statistics, it is not possible to extract specific diagnostic data.

The ICD undergoes continual revision and expansion. The current version, ICD-8, was adopted in 1965. The United States and some other countries expanded the ICD code into a system called ICDA which provides greater detail and specificity. The lates edition, HICDA-II, was published in 1973. These systems are among the most widely used but do not allow access to refined problems, since they were not designed with detailed item analysis in mind. Rather, they were designed to collect national and international mortality and morbidity data.

Classification systems which provide only a series of categories into which various medical concepts can be placed do not meet the specific requirements of fields such as pathology. The first major nomenclature system was developed by the College of American Pathologists (CAP) and published in 1965. The Systematized Nomenclature of Pathology is essentially a four axis system with all pertinent and useful terms grouped into four basic categories: Topography, Morphology, Etiology, and Function. Each term is uniquely identified by a four digit number prefixed by an alphabetic category identifier (T, M, E and F).

In order to be useful in fields other than pathology, expansion of the SNOP coding system was required. It was apparent that there was a distinct need for a more detailed nomenclature useful to all of medicine. As a result, the College of American Pathologists developed and published in 1976 the Systematized Nomenclature of Medicine (SNOMED).

SNOMED is compatible with the SNOP since it is amenable to computer processing, modular and open-ended, and it permits the addition of new dimensions without destroying older categorized and coded data. Its inherent flexibility enables it to keep pace with the continuing changes in the medical field. The original four fields of SNOP (Topography, Morphology, Etiology and Function) are restructured and expanded using a five-digit identifier. Two new fields, Disease and Procedures, have been added to produce a six-axis system which represents a complete hierarchical structure for human health and health care.

The Topography field provides a structured nomenclature for anatomy. The Morphology field, contains terms that describe or name pathological changes or processes occurring in cells, tissues or organs. It is designed for medical specialties that make gross or microscopic observations on tissues or organ systems of the human body. The Etiology field identifies agents or causes of disease or morphological change. These include microbiologic and other living agents, chemicals, radioisotopes, small groups of carcinogens, and industrial products or materials. Also included in this field are physical events or injuries. The Function field identifies body functions and physiologic units of the major organ systems. Signs and symptoms of disease comprise a major portion of the terms found in the Function field.

The four basic axes contain the nomenclature components of disease so that multiple combinations when added together yield a disease notion or concept. The following example illustrates this concept (a horizontal term linkage).

T		M		E		F		D
Lung	+	Granulomas	+	Mycobacterium	+	Fever	=	Tuberculosis

The fifth field in SNOMED, Disease, provides an organized list of classes diseases, complex disease entities, and syndromes. This field could be used as the classification extension of the other four nomenclature fields since it allows the regrouping of the diagnostic elements under a single title or code. The final SNOMED field, Procedure, is a list of administrative, diagnostic, therapeutic, and preventive procedures used in a health care system. Figure 4-17 presents the Section Identifiers, which are the broadest level of indexing, for each of the six SNOMED fields. Each of these sections is expanded using terms uniquely identified by an additional four digits.

The various SNOMED fields may be incorporated into a dictionary or program for a computer-based collection of information. Although there are nearly 40,000 unique terms in the SNOMED system, a smaller subset of mini-glossaries would provide sufficient diagnostic and procedural vocabulary to satisfy CTSS needs. Examples applicable to CTSS would include lists of diagnoses, tumor registries, autopsy pathology, or a compendium of behavioral disorders, all of which would simplify the task of looking up codes, entering data, and retrieving information.

At the same time that SNOMED was under development, the World Health Organization (WHO) published the International Classification of Diseases for Oncology (ICD-O). The ICD-O provides an internationally agreed upon system for the coding of neoplasms by specific histologic type as well as topographic site. It is based on the Manual of Tumor Nomenclature and Coding (MONTAC) which was based on ICD-8, and Sections 8 and 9 of Morphology from SNOP. ICD-O contains two principal numerical sections, Topography and Morphology. The ICD-O Morphology section has been included in SNOMED as Sections 8 and 9 in Morphology.

FIGURE 4-17 (1)

SNOMED Section Identifiers

TOPOGRAPHY INDEX

SECTION 0:	GENERAL BODY TOPOGRAPHY; INTEGUMENTARY, HEMATOPOIETIC AND LYMPHATIC SYSTEMS
SECTION 1:	MUSCULOSKELETAL SYSTEM AND SOFT TISSUES
SECTION 2:	RESPIRATORY SYSTEM
SECTIONS 3 & 4:	CARDIOVASCULAR SYSTEM
SECTIONS 5 & 6:	DIGESTIVE SYSTEM
SECTIONS 7 & 8:	GENITOURINARY SYSTEMS AND FETAL STRUCTURES
SECTION 9:	ENDOCRINE SYSTEM
SECTION X:	NERVOUS SYSTEM AND SPECIAL SENSE ORGANS
SECTION Y:	TOPOGRAPHIC REGIONS

MORPHOLOGY INDEX

SECTION 0:	GENERAL NONSPECIFIC MORPHOLOGY
SECTION 1:	TRAUMATIC ABNORMALITY
SECTION 2:	DEVELOPMENTAL MALFORMATION AND ABNORMAL PRODUCT OF CONCEPTION
SECTION 3:	MECHANICAL ABNORMALITY
SECTION 4:	INFLAMMATION AND FIBROSIS
SECTION 5:	DEGENERATION, NECROSIS, DEPOSITION, DYSTROPHY AND ATROPHY
SECTION 6:	CHROMOSOMAL AND CYTOLOGIC ALTERATIONS
SECTION 7:	GROWTH AND MATURATION ALTERATION
SECTIONS 8 & 9:	NEOPLASMS

ETIOLOGY

SECTION 0:	GENERAL ETIOLOGY
SECTIONS 1 & 2:	BACTERIA AND RICKETTSIAE
SECTION 3:	VIRUSES
SECTION 4:	FUNGI, PARASITES, INSECTS AND ANIMALS
SECTIONS 5 & 6:	CHEMICALS—CHEMICAL ELEMENTS—CHEMICAL PRODUCTS
SECTIONS 7 & 8:	DRUGS AND BIOLOGICALS
SECTION 9:	PHYSICAL AGENTS

FUNCTION INDEX

SECTION 0:	GENERAL BODY FUNCTION AND DYSFUNCTION
SECTIONS 1 & 2:	FUNCTION AND FUNCTIONAL UNITS OF METABOLISM AND THE ENDOCRINE SYSTEM
SECTION 3:	FUNCTION AND ABNORMAL FUNCTION ASSOCIATED WITH REPRODUCTION
SECTION 4:	FUNCTION AND FUNCTIONAL UNITS OF THE IMMUNE SYSTEM
SECTION 5:	FUNCTION AND ABNORMAL FUNCTION OF THE HEMATOPOIETIC SYSTEM
SECTION 6:	FUNCTION AND ABNORMAL FUNCTION OF THE DIGESTIVE AND URINARY TRACTS
SECTION 7:	FUNCTION AND ABNORMAL FUNCTION OF THE CARDIOVASCULAR AND RESPIRATORY SYSTEMS
SECTION 8:	FUNCTION AND ABNORMAL FUNCTION OF THE NERVOUS AND MUSCULOSKELETAL SYSTEMS
SECTION 9:	FUNCTION AND ABNORMAL FUNCTION OF THE PSYCHE AND THE SEXUAL STATE
SECTION X:	FUNCTION AND ABNORMAL FUNCTION OF THE EYE, EAR AND THROAT
SECTION Y:	ENVIRONMENTAL AND FORENSIC CIRCUMSTANCES SURROUNDIN INJURY OR DEATH

FIGURE 4-17 (2)
SNOMED Section Identifiers

DISEASE INDEX

SECTION 0:	INFECTIOUS AND COMMUNICABLE DISEASES
SECTION 1:	METABOLIC AND NUTRITIONAL DISEASES AND SYNDROMES
SECTION 2:	DISEASES AND SYNDROMES OF THE ENDOCRINE AND REPRODUCTIVE SYSTEMS
SECTION 3:	COMPLEX DISEASES AND SYNDROMES OF THE SKELETAL SYSTEM, SKIN AND CONNECTIVE TISSUES
SECTION 4:	COMPLEX DISORDERS, SYNDROMES AND DISEASES OF THE HEMATOPOIETIC AND IMMUNE SYSTEMS
SECTION 5:	MULTIPLE SYSTEM MALFORMATION SYNDROMES AND CHROMOSOMAL DISEASES
SECTION 6:	DISEASES AND SYNDROMES OF THE DIGESTIVE AND URINARY TRACTS
SECTION 7:	DISEASES AND SYNDROMES OF THE CARDIOVASCULAR AND RESPIRATORY SYSTEMS
SECTION 8:	DISEASES AND SYNDROMES OF THE NERVOUS AND MUSCULAR SYSTEMS
SECTION 9:	EMOTIONAL, MENTAL AND SEXUAL DISEASES AND SYNDROMES
SECTION X:	COMPLEX DISEASES AND SYNDROMES OF THE EYE, EAR, NOSE AND THROAT
SECTION Y:	GENERAL CATEGORY OF CLINICAL DISEASES AND SYNDROMES

PROCEDURE INDEX

SECTION 0:	GENERAL MEDICAL AND ADMINISTRATIVE PROCEDURES
SECTION 1:	OPERATIVE AND ANESTHETIC PROCEDURES
SECTIONS 2-3-4:	LABORATORY PROCEDURES
SECTION 5:	HEMATOPOIETIC, IMMUNOLOGIC AND DERMATOLOGIC PROCEDURES
SECTION 6:	DIGESTIVE AND URINARY TRACT PROCEDURES
SECTION 7:	CARDIOVASCULAR AND RESPIRATORY SYSTEM PROCEDURES
SECTION 8:	NEUROMUSCULOSKELETAL SYSTEM AND SPECIAL SENSE ORGAN PROCEDURES
SECTION 9:	PROCEDURES RELATED TO THE PSYCHE, SEX AND REPRODUCTION
SECTION X:	RADIOGRAPHY, RADIATION THERAPY, NUCLEAR MEDICINE AND ULTRASONIC PROCEDURES
SECTION Y:	NURSING, DIET AND HOME CARE PROCEDURES

Two additional coding systems will be available for use in January 1979, ICD-9 and ICD-9-CM. ICD-9 is the latest version of ICD which includes only minor changes form ICD-8. ICD-9-CM is derived from ICD-9 but is oriented toward clinical medicine.

4.3.2 Laboratory Animal Data Bank (LADB)

LADB users include the biomedical community and those government agencies that have responsibilities associated with large scale animal testing. Regulatory and other agencies concerned with public health which make decisions on the latent effects resulting from long-term, low-level exposure to chemical substances, would find LADB useful. The primary objectives of LADB are to provide a system which will facilitate: 1) the selection of appropriate species or strains for a laboratory experiment; 2) the comparison of base-line values between animal colonies; 3) the establishment of reliable base-line values; 4) the collection and monitoring of the incidence of spontaneous diseases in control animals; 5) the information required to design experiments, and 6) the development of animal models which would describe the characteristics of various strains or species that makes them suitable for specific research projects.

Unlike the proposed CTSS which would require laboratories to submit data in a standard format, LADB accepts experimental data in any form provided that the required data elements are recorded. Submitted information is analyzed by LADB personnel and converted to a set of standardized data elements on preformatted forms. These forms are keyed into transactions which are then used to update the system. LADB personnel are responsible for making judgments concerning the suitability of donated information and the transformation of descriptive codes and units of measure from one form to another.

The LADB data base consists of a Base-Line Data File and a Strain File. The Strain File is textual, containing descriptive information such as animal characteristics and origin. The Base-Line File, which is designed to provide data not readily available in published literature, is mainly numeric and contains base-line values on laboratory animal control groups.

The records in the LADB data base emphasize animal groups or colonies which are composed of the same strain, source, and supplier, and which are maintained under the same environmental and husbandry conditions. (This contrasts with the CTSS which would emphasize the various dose groups, including the control group, within an experiment). In LADB, there is no way to associate a control group with a particular experiment. Environmental information consists of data elements related to temperature, humidity, ventilation, lighting, animal housing, and sterilization. Husbandry information includes data elements relating to water, feed, bedding, and conditioning (vaccination, quarantine, etc.). Data elements associated with identification include species name, strain name, type of control, source of animal, animal supplier, and breeding type and status. Demographic information includes sex, age, test year, and location (city, state, altitude, latitude and longitude). Biomedical information consists of data elements related to clinical chemistry, hematology, and pathology. Pathology data includes organ weights, organ topography, manner of death, tissues examined, abnormality, lesion duration, intensity, and incidence, etiology and status. The codes are relatively limited and were developed in-house. The pathology data submitted to LADB is reviewed by staff members and coded. To enhance the on-line analysis capability, the original pathology observation is also recorded in the file. Users select data based on the limited set of codes, but they have the option of analyzing the full-text pathology report. LADB is open-ended so that future, additional categories of data can be added to the system without disrupting the current structure and content.

The access portion of the system was designed so that formal training in computer retrieval methodology would not be necessary. Using the search and retrieval aspects of LADB, a scientist may: 1) select and examine base-line data for various physiologic and pathologic values; 2) determine the environmental and husbandry conditions for each animal group selected; 3) statistically analyze the obtained data; and 4) print the data retrieved as distributions, such as graphs, histograms, summations, or complete reports.

The user may conduct LADB search and retrieval sessions in either a prestructured or direct mode. The structured mode eliminates the need for extensive user training. It is menuselection oriented; the system guides the user through the various search and retrieval features using a set of predefined options at each node or decision point. The system displays the possible options and prompts the user for an answer at each node. This method is time-consuming, but it eliminates the need to refer to a user manual in order to access the system. Figure 4-19 illustrates portions of a structured LADB terminal session. The direct search mode is available for users with extensive LADB experience. In this mode, the user enters the desired command without any prompting or display of options. The computational and reporting capability within LADB is provided by a commercial statistical package, SPSS (Statistical Package for the Social Sciences). From user specifications, LADB constructs the required SPSS input and displays the results returned from SPSS to the user. LADB is currently being tested and modified and is available only to those users that have supplied data. Once testing and modifications are completed, it will be available to the general public for a modest fee.

4.3.3 Toxicology Data Management System (TDMS)

Because of areas of mutual interest between NCTR and NCI, a joint effort is currently underway to develop an integrated computer-based system to support the full spectrum of laboratory animal testing. The system, known as the Toxicology Data Management System, is compatible with the managment and processing needs of NCTR and NCI related to the collection, maintenance, analysis and reporting of bioassay data. The TDMS is

FIGURE 4-18(1)

LADB Terminal Session

```
 DATA AVAILABLE FOR STATISTICAL ANALYSES ARE GROUPED
 BY COMBINATIONS OF AGE (OR AGE GROUPINGS), TEST YEAR, AND SEX
 FOR EACH DATA ELEMENT (E.G. HCT, BUN, WBC) WITHIN A COLONY.

 THERE ARE 23   COMBINATIONS OF THESE IDENTIFIERS FOR YOUR SEARCH
 DO YOU WANT TO SELECT GROUPS BY AGE, SEX, OR TEST YEAR?
 ENTER YES OR NO
    / N
 ENTER A DATA ELEMENT ABBREVIATION
    / RBC
 CHOOSE LADB STATISTICAL SERVICE BY NUMBER:
   1. DISTRIBUTIONS (SUMMARY STATISTICS, FREQUENCY HISTOGRAM &/OR TABLES)
   2. CROSSTABULATION & CHI-SQUARE TEST WITH MEASURES OF ASSOCIATION
      OPTIONAL
   3. BREAKDOWN (ANY COMBINATION OF COLONY(S), SEX, AGE, AND TEST YEAR)
   4. T-TEST
   5. ONE-WAY ANALYSIS OF VARIANCE WITH STATISTICS OPTIONAL
      (NOT AVAILABLE)
   6. SCATTERPLOT WITH LINEAR REGRESSION AND CORRELATION OPTIONAL
      (NOT AVAILABLE)
   7. RETURN TO "SELECT DATA GROUPINGS"
   8. RETURN TO "CHOOSE BASIC LADB SERVICE"
    / 3

DO YOU REQUIRE INFORMATION ON THE USE OF THE BREAKDOWN PROCEDURE?
ANSWER YES OR NO
   / YES
THE BREAKDOWN PROCEDURE CALCULATES MEANS, STANDARD DEVIATIONS,
AND NUMBER OF OBSERVATIONS FOR A DATA ELEMENT CATEGORIZED
(BROKEN DOWN) BY A COMBINATION OF THE VARIABLES COLONY NUMBER,
SEX, AGE CATEGORY, AND TEST YEAR. AT YOUR OPTION, EACH VARIABLE
CAN BE BROKEN OUT SEPARATELY (ONE-WAY BREAKDOWN) OR WITH RESPECT
TO THE ONE PRECEEDING IT (HIGHER-ORDER BREAKDOWN).

YOUR DATA ELEMENT RBC   , CAN BE BROKEN DOWN WITH RESPECT TO THE
FOLLOWING VARIABLES:
  1. COLONY NUMBER
  2. SEX
  3. AGE CATEGORY
  4. TEST YEAR
MEANS, STANDARD DEVIATIONS, AND NUMBER OF OBSERVATIONS FOR
RBC   , WILL BE BROKEN DOWN IN THE ORDER YOU SPECIFY.
CHOOSE ONE OR MORE OF THE VARIABLES, SEPARATING YOUR
CHOICES WITH COMMAS.
   / 1,2
CHOOSE BREAKDOWN OPTION BY NUMBER:
  1. ONE-WAY BREAKDOWN
  2. HIGHER-ORDER BREAKDOWN
   / 2
```

FIGURE 4-18 (2)

LADB Terminal Session

```
SPSS/ONLINE V4.0


- - - BREAKDOWN - - -


END OF FILE ON FILE INDATA
AFTER READING    189 CASES FROM SUBFILE NONAME

CRITERION VARIABLE   RBC        RBC IN 10**6 PER CU MM
    BROKEN DOWN BY   COLN       COLONY NUMBER
                BY   SEX        SEX

    VARIABLE         CODE         MEAN  STD. DEV.       N VALUE LABEL

FOR ENTIRE POPULATION            6.631       .628    250

COLN                   6.        6.661       .701    155
 SEX                   1.        6.512       .633     78 MALE
 SEX                   2.        6.813       .737     77 FEMALE

COLN                   9.        6.582       .484     95
 SEX                   1.        6.483       .435     47 MALE
 SEX                   2.        6.678       .515     48 FEMALE

TOTAL CASES =      250

SINCE MULTIPLE OBSERVATIONS ARE OFTEN OBTAINED FROM EACH ANIMAL
OVER TIME, THE ABOVE STATISTICS ARE BASED ON THE NUMBER OF VALID
CASES  (OBSERVATIONS) SHOWN ABOVE OBTAINED FROM 134
INDIVIDUAL ANIMALS.

=======================================================================

CHOOSE YOUR NEXT STEP BY NUMBER:
  1. SAME DATA ELEMENT
  2. ANOTHER DATA ELEMENT
  3. RETURN TO "SELECT DATA GROUPINGS"
  4. RETURN TO "CHOOSE BASIC LADB SERVICE"
   / 1
```

important to the CTSS in that the proposed TDMS could possibly combine four of the CTSS sybsystems (Data Collection, Data Submission, Storage and Conversion, and Detailed Analysis and Evaluation) into one integrated system, and it would eliminate some of the transcription and transformation problems inherent in separate but interdependent CTSS subsystems.

The TDMS includes design characteristics that are important ingredients in developing a multi-component yet integrated system to monitor and control animal studies. The system is designed to be responsive to all levels of management during the course of an animal experiment. A primary goal of the TDMS is to provide users with an information feed-back loop whereby they can monitor and control an experiment on a daily basis. Data that are entered into the system are processed with existing data and the result is a set of review reports that are sent to users the next day. In this way, problems or inconsistencies that may require a protocol change can be identified quickly.

The TDMS is designed to minimize errors during data collection. Upon detection of an error, the system will prompt the operator for appropriate corrective action and document the action in accordance with the Good Laboratory Practices. The hardware has been designed to maximize system reliability and minimize the impact of any component failure.

In order to satisfy each experiment's protocol requirements, the TDMS incorporates flexible design techniques which accommodate user needs related to physical and analytical facilities, experiment objectives, end points, test species, etc. The system is being developed so as to be transferrable to other government agencies, academia, or industrial facilities with similar research/testing information requirements.

Data among the TDMS modules are aggregated under a common data base structure that will facilitate data tracking/audit and data analysis.

The TDMS will provide the user with automated procedures throughout the course of an animal experiment, including:

- Documentation of each compound nominated, reviewed, and recommended

- Analysis of each new experiment protocol and projection of resource requirements for conducting the test

- Allocation (selection and recording) of animals to the experiment

- Collection of weights, food consumption, and observations during the conduct of the experiment

- Recording of pathology results
- Maintenance of a complete experiment status summary
- Generation of a draft report which will aid in the development of a published final report

The TDMS consists of various interrelated modules that provide this support, including:

- Compound Management System (CMS)
- Protocol Analysis System (PAS)
- Experiment Status System (ESS)
- Experiment Information System (EIS)
- Post Experiment Information System (PEIS)
- Non-Animal Data System (NADS)
- Query Language Processor (QLP)

These modules are discussed in more detail below:

Compound Management System (CMS)

The CMS is designed to support the requirements of NCI which must consider a large amount of chemical testing data. The major objective of CMS is to track the decisionmaking procedures for each nominated compound from the initial consideration to the final selection for testing.

Users may query the system in an interactive mode to determine the status and/or review actions of a given compound and receive an immediate answer. Standard reports will summarize the results of actions taken during a particular review meeting. The CMS will also assist the chemical selection process by informing personnel of overdue reviews and preparing agendas for various working groups and committees.

Protocol Analysis System (PAS)

The PAS will provide automated support from the selection of a compound to the initiation of an experiment. Upon selection of a compound for testing, PAS will develop a logical model or profile of the experiment. A design group will determine the types of experiments to be conducted, route of administration, number of doses, animals, strains, etc.

The PAS will also record facility data for an experiment. This information will include contractor name, location, type of ventilation, type of lighting, method of sterilization, etc. The module will also permit projections of required resources such as quantity of feed, quantity of test compound, quantity of bedding, number of animals, number of cages, etc., all of which are needed to conduct the experiment properly.

The PAS module will establish projected dates for compound procurement, animal delivery, and experimental events. Once the protocol is developed, several reports will be generated for review by management. After the protocol is approved, PAS will initiate the appropriate Experiment Status Summary activities.

Experiment Status System (ESS)

The ESS provides a current operational status for each experiment in progress by receiving update information from other TDMS modules, including the Experiment Information System, the Post Experiment Information System, and the Non-Animal Data System. The information it receives is in summary form. As the size of other files get larger, quick reviews can be accomplished by simply querying the ESS files. This will minimize the need for accessing the larger EIS and PEIS support files to review the status of an experiment and other summary parameters.

The ESS will allow users to compare and check projected dates against actual dates and will document and report actual events such as the number of animals remaining, number of animals processed by pathology, number of tumors, and backlogs and workloads for necropsy. ESS will provide managers with the ability to monitor the financial status of an experiment as well as the scientific status. Once a contractor is selected and the resource projections made, budgetary information relating to the experiment will be entered into the system. This will enable ESS to effectively monitor the month by month expenditures against the budgeted dollars for each experiment.

The ESS will be able to generate a report summarizing the entire experiment which will aid in the development of a final report for each compound tested.

Experiment Information System (EIS)

The EIS will monitor the animals during their lifetime on an experiment. Included in the system will be body weights, food consumption, clinical signs, etc. The EIS includes several categories of output reports for management personnel and scientific investigators which will provide an early warning capability by indicating abnormal or unexpected trends, such as exceptional weight loss or animal loss, in time for example to implement changes to the experimental design. The EIS module provides data gathering support from the time that the experiment is initiated and dosing begins, until all the animals are dead or removed.

The most important aspect of the EIS is the automated source data collection facility which will facilitate adherence to established protocols and procedures, and will reinforce the integrity of the data collected. The EIS is designed to meet the intent of the Good Laboratory Practices guidelines with regard to laboratory procedures and data control.

The hardware associated with the EIS includes a microcomputer-based system consisting of a microprocessor, floppy disk storage, a display terminal, and an electronic balance scale. The EIS data collection system is intended to operate independently of any host computer. At the start of an experiment, the PAS/ESS, through the host computer, will generate an animal room record on a floppy disk. The floppy disk will record all the data associated with all the animals in a particular room during the course of the experiment.

Data collection begins when an animal caretaker inserts the floppy disk for an animal room into the microprocessor and identifies himself/herself and each of the animals processed. As the animal caretaker weighs the old feeder, the new feeder, and each animal on the electronic balance, the weights will be automatically recorded on the floppy disk, thus eliminating transcription errors. Since the floppy disk contains the complete record for an animal, it can provide information for editing each new entry. For example, if an animal's new weight is above or below the limit for weight fluctuation, EIS will promt the caretaker at that point and request a second weighing for verification. These real-time edits improve the quality of data captured and enforce proper data collection procedures by animal caretakers.

Clinical observations are automatically recorded on the floppy disk by an animal caretaker touching a particular area of a preformatted display terminal. The display terminal presents the possible observations for a particular experiment. The animal caretaker merely touches the areas of the screen where the observation acronyms are displayed to record appropriate observations. The EIS contains program checks which prevent illegal data entry. e.g., a clinical sign for an animal previously recorded as dead.

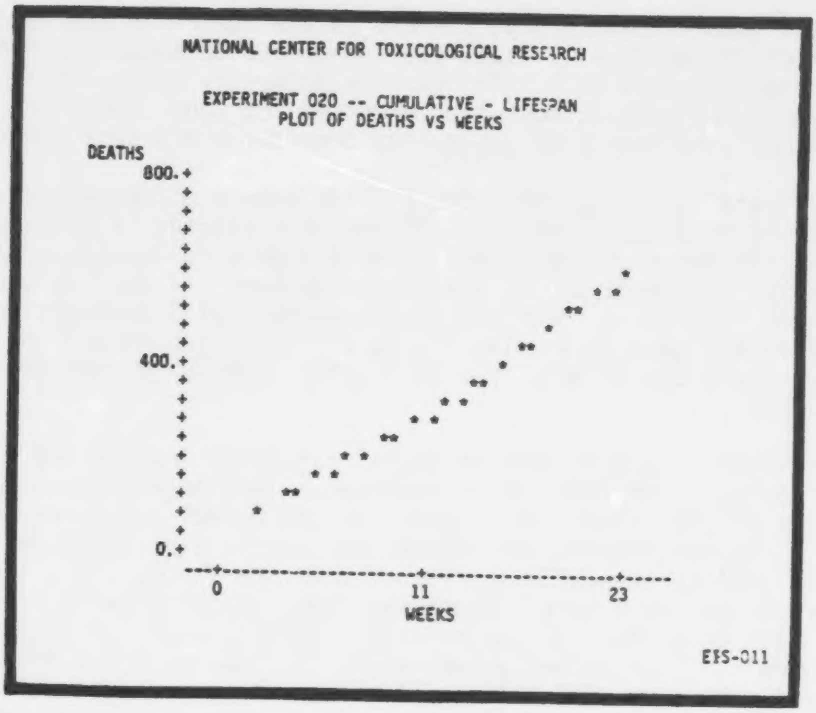
Information most recently entered on the floppy disk is used to update the master file at the central computer site. Based on the new information, summary reports are produced by the central computer and distributed to management personnel and scientific investigators. Figure 4-19 illustrates some of the EIS summary reports.

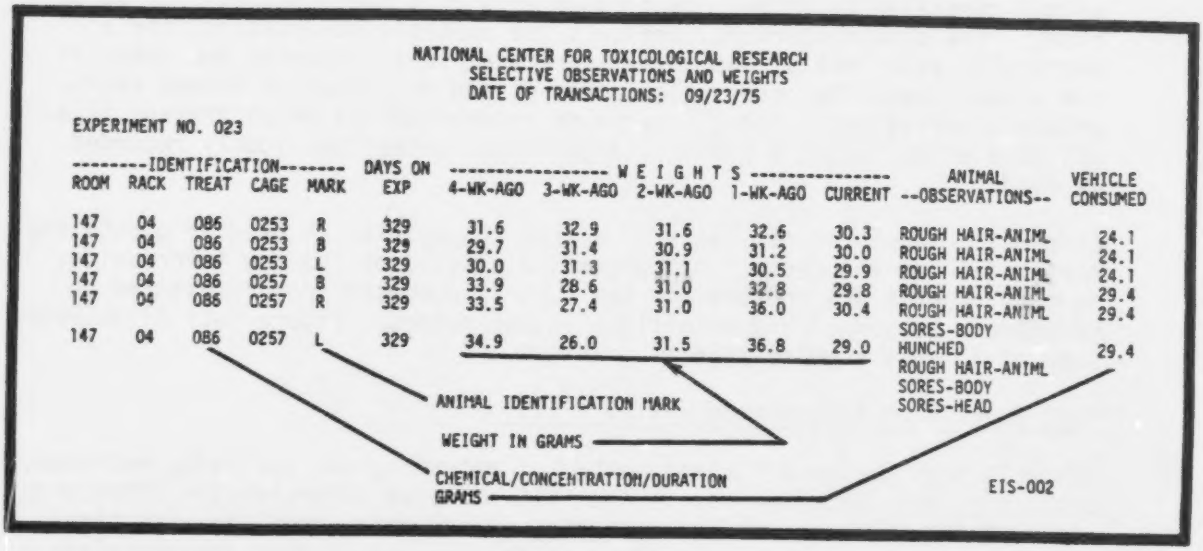
Post Experiment Information System (PEIS)

The PEIS provides an efficient method of recording and analyzing necropsy, pathology, and histology data. The PEIS includes comprehensive procedures and controls that insures the recording of accurate, complete, and timely data beginning with the death of an animal and ending when the pathology

FIGURE 4-19 (1)

Sample EIS Summary Reports





```
                        NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH
                              SELECTIVE OBSERVATIONS AND WEIGHTS
                              DATE OF TRANSACTIONS:  09/23/75

EXPERIMENT NO. 023

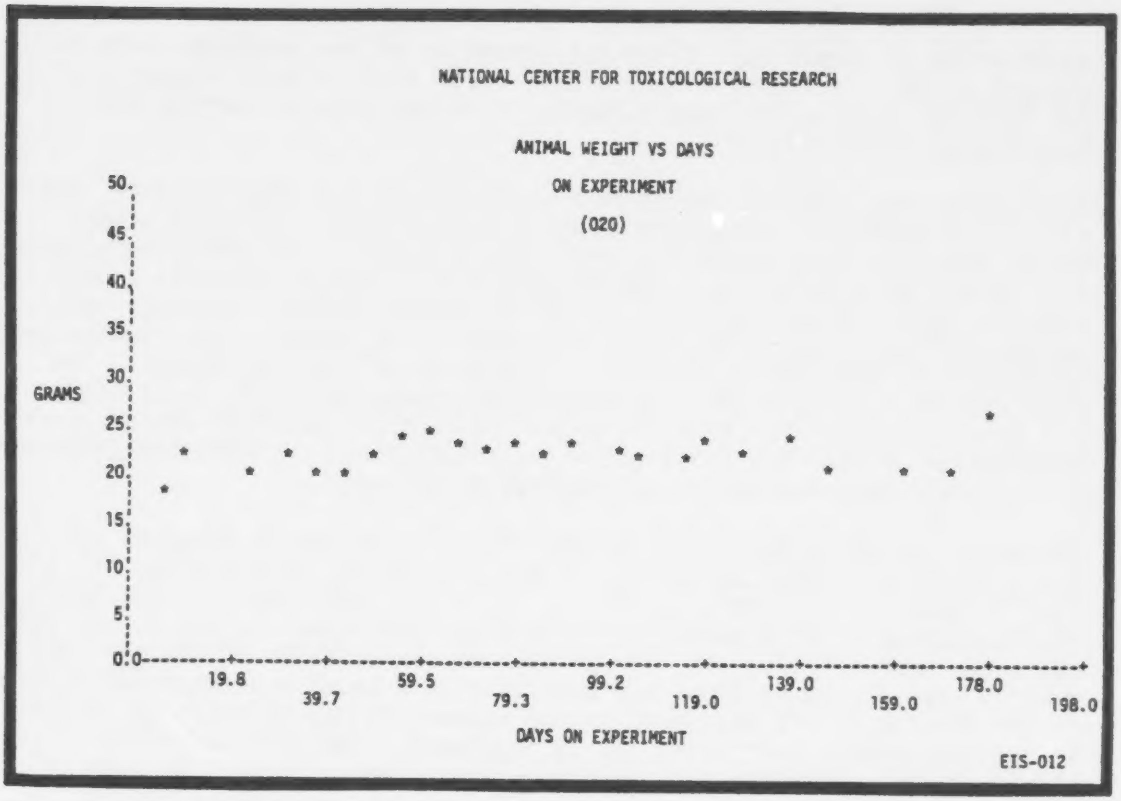
--------IDENTIFICATION-------  DAYS ON  ---------------- W E I G H T S ---------------     ANIMAL       VEHICLE
ROOM  RACK  TREAT  CAGE  MARK     EXP    4-WK-AGO  3-WK-AGO  2-WK-AGO  1-WK-AGO  CURRENT --OBSERVATIONS--  CONSUMED

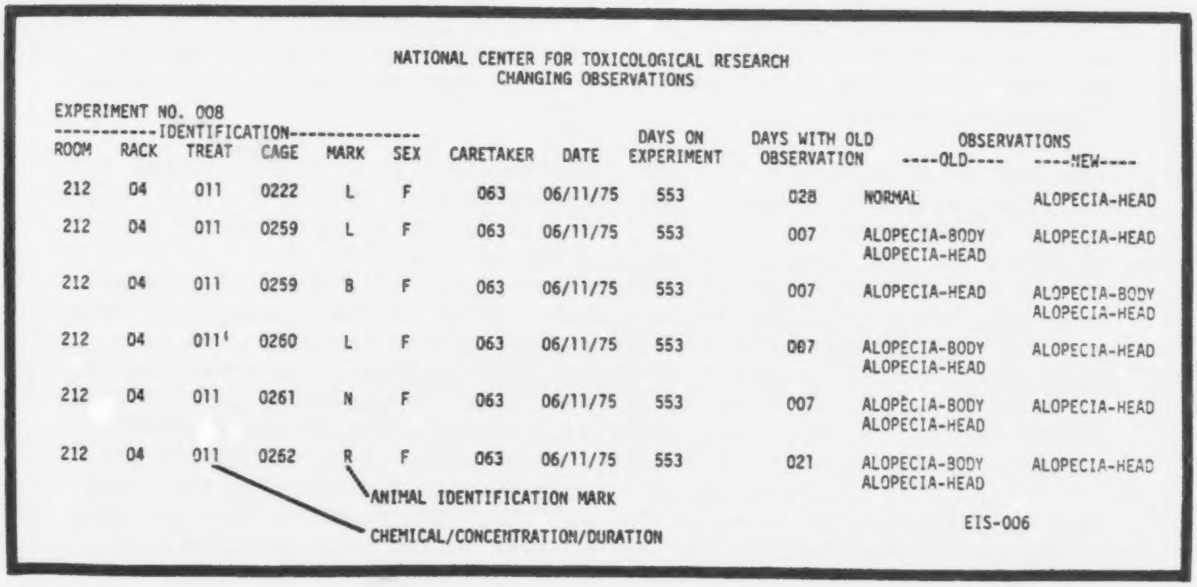
147    04    086   0253   R       329     31.6      32.9      31.6      32.6      30.3   ROUGH HAIR-ANIML     24.1
147    04    086   0253   B       329     29.7      31.4      30.9      31.2      30.0   ROUGH HAIR-ANIML     24.1
147    04    086   0253   L       329     30.0      31.3      31.1      30.5      29.9   ROUGH HAIR-ANIML     24.1
147    04    086   0257   B       329     33.9      28.6      31.0      32.8      29.8   ROUGH HAIR-ANIML     29.4
147    04    086   0257   R       329     33.5      27.4      31.0      36.0      30.4   ROUGH HAIR-ANIML     29.4
                                                                                         SORES-BODY
147    04    086   0257   L       329     34.9      26.0      31.5      36.8      29.0   HUNCHED              29.4
                                                                                         ROUGH HAIR-ANIML
                                                                                         SORES-BODY
                                                                                         SORES-HEAD
```

ANIMAL IDENTIFICATION MARK
WEIGHT IN GRAMS
CHEMICAL/CONCENTRATION/DURATION
GRAMS
EIS-002

FIGURE 4-19 (2)

Sample EIS Summary Reports





NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH
CHANGING OBSERVATIONS

EXPERIMENT NO. 008

IDENTIFICATION										OBSERVATIONS	
ROOM	RACK	TREAT	CAGE	MARK	SEX	CARETAKER	DATE	DAYS ON EXPERIMENT	DAYS WITH OLD OBSERVATION	OLD	NEW
212	04	011	0222	L	F	063	06/11/75	553	028	NORMAL	ALOPECIA-HEAD
212	04	011	0259	L	F	063	06/11/75	553	007	ALOPECIA-BODY ALOPECIA-HEAD	ALOPECIA-HEAD
212	04	011	0259	B	F	063	06/11/75	553	007	ALOPECIA-HEAD	ALOPECIA-BODY ALOPECIA-HEAD
212	04	011	0260	L	F	063	06/11/75	553	007	ALOPECIA-BODY ALOPECIA-HEAD	ALOPECIA-HEAD
212	04	011	0261	N	F	063	06/11/75	553	007	ALOPECIA-BODY ALOPECIA-HEAD	ALOPECIA-HEAD
212	04	011	0262	R	F	063	06/11/75	553	021	ALOPECIA-BODY ALOPECIA-HEAD	ALOPECIA-HEAD

ANIMAL IDENTIFICATION MARK

CHEMICAL/CONCENTRATION/DURATION

EIS-006

examination is completed. Since the integrity of the pathology data is crucial to the results of a laboratory animal test, a major emphasis of the PEIS has been on the development of thorough data collection and maintenance procedures.

Gross pathology data include terminal body weight and organ weights, overall tissue condition and abnormal gross observations. For each target organ, the PEIS records findings relating to color, size consistency, shape, and surface charcteristics. Additionally, if a mass is present, a description and appropriate dimensions can be recorded. Microscopic data consist of abnormal pathological findings including grade, type, stage, subtopography, lesion count, presence of autolysis, and cause of death diagnosis. The PEIS will also support data concerned with blood chemistry, hematology, and chemical analyses. To provide quality control, the PEIS records such information as the date and time an event took place, and the identification of personnel responsible for an examination or test.

The data collection mechanisms of the PEIS are similar to those of the EIS: i.e., automated source data entry, a microprocessor, floppy disk, CRT display screen, and electronic balance. The floppy disk contains the complete PEIS census data for a number of animals and initiates a gross or microscopic pathology examination. For each animal, an abbreviation of the most frequently encountered findings are displayed on a touch sensitive CRT screen. If the finding is not displayed on the screen, it may be recorded by typing in the appropriate code using the CRT keyboard. The data collection system also includes a "scratch pad" feature which allows examiners to type in comments in a free-text mode. Having all the data associated with an animal available in a real-time mode allows instantaneous error checking, data validation, control, and reporting. An error such as a "mistouch" is corrected by touching a designated control point and then retouching the erroneous finding. The notification of the error and its correction will be recorded in the PEIS system as required by the GLP guidelines. At any time during the experiment, an investigator can review the findings on the display screen.

The problem of developing a comprehensive, consistent coding scheme for recording pathology findings has been addressed by the TDMS staff. As stated elsewhere in this report (Sec. 4.3.1), pathology findings lead to somewhat subjective observations (expressed in English prose). In order to minimize these problems of consistency, standard recording schemes should be employed. PEIS has adopted a subset of the Systematized Nomenclature of Pathology (SNOP) as the data recording language with some additional codes to adapt it to rodent test species. The resulting set of descriptions is referred to as "mini-SNOP" and contains approximately 4,000 entries. A relatively small number of differenct observations account for the majority of findings reported for a particular target tissue and mini-dictionaries, which can be displayed on a screen, have been developed which represent the most probable findings for each subtopography. When findings are not present in the most probable list, they are chosen from the full mini-SNOP dictionary and typed in.

Once the examination is completed, the information on the floppy disk is transmitted to the central computer to update the master files. Summary reports for review by investigators are available both locally and from the central site. The most frequently used reports required for immediate analysis are generated locally because of the need for a short response time. These PEIS reports include the results of gross and microscopic analysis for each animal and incidence of abnormal findings by treatment group. Larger reports not requiring a short response time such as quality control, comprehensive tabulations and sorts, and cross-experiment summaries are produced at the central computer site and sent to the appropriate investigator or manager. Figure 4-20 illustrates several PEIS reports in use at NCTR.

Non-Animal Data System (NADS)

The NADS is designed to support the data generated as the result of chemical and microbiological tests performed on the laboratory animals and from the facilities used in support of the experiment. The testing compound is analyzed for homogeneity, composition, temperature, stability, and other properties. Lab analyses are performed on diets or doses to insure proper mixing, concentration, and exposure. Animal feed data are recorded on nutrient contents and contaminants such as heavy metals, pesticides, and chlorinated hydrocarbons. The system will provide standardization for operational procedures which will outline the collection and recording of these analyses according to the Good Laboratory Practices.

Microbiological surveillance results recorded by NADS include bacteriology, virology, mycology and parasitology data. The number and type of microorganisms present in the experimental animals, the type of animal cages, the type of animal bedding, and other items relevant to their environment are included in the record.

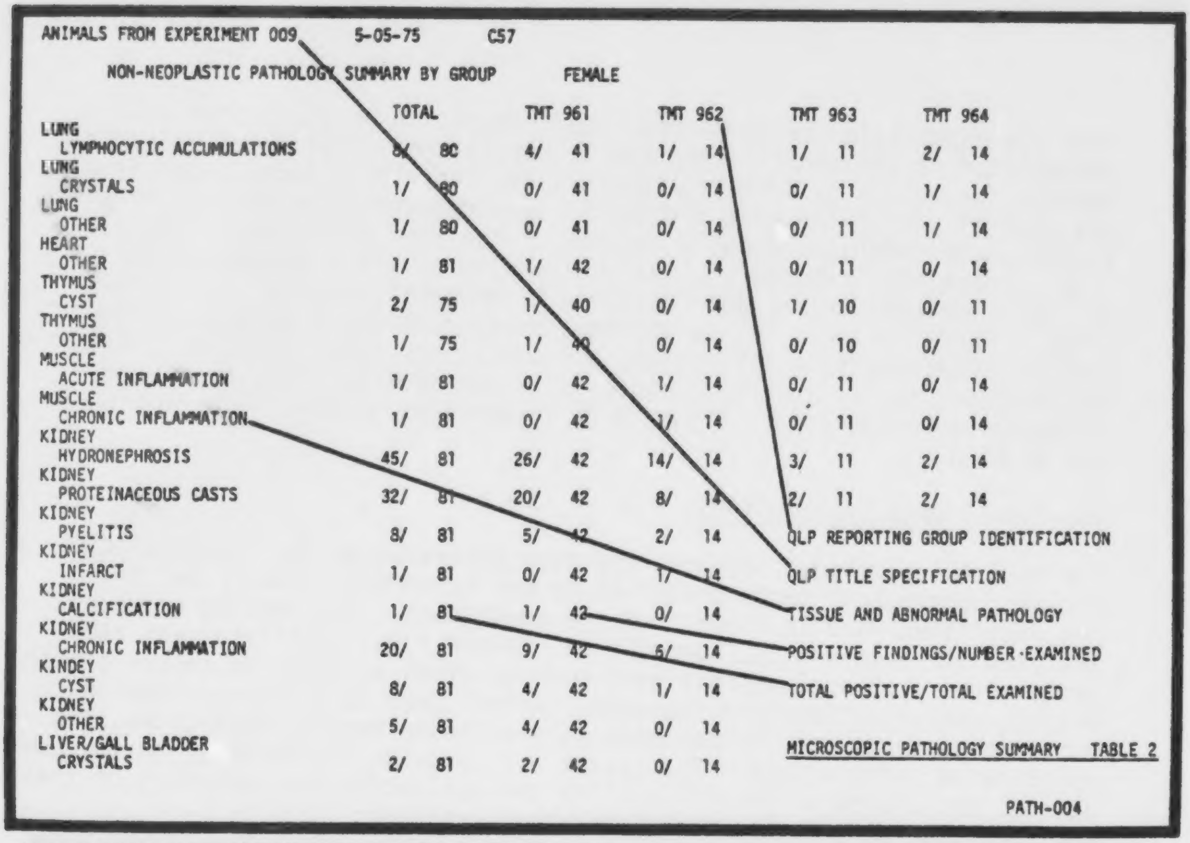
The supporting chemical and microbiological data will be available for investigation with other collected by the TDMS. NADS will generate a number of routine reports including schedules for conducting analyses and for monthly progress reports.

Query Language Processor (QLP)

The QLP is designed to interrogate and retrieve information about all the data elements collected by the other TDMS modules. The QLP retrieval language allows users to structure requests based on any data element in the TDMS. Because of the interactive retrieval capability, ad hoc as well as routine requests for historical and active information are answered in a minimal amount of time. The QLP to be used in the TDMS will be an enhancement of the current QLP in use at NCTR.

FIGURE 4-20 (1)

Sample PEIS Reports



```
ANIMALS FROM EXPERIMENT 009     5-05-75     C57

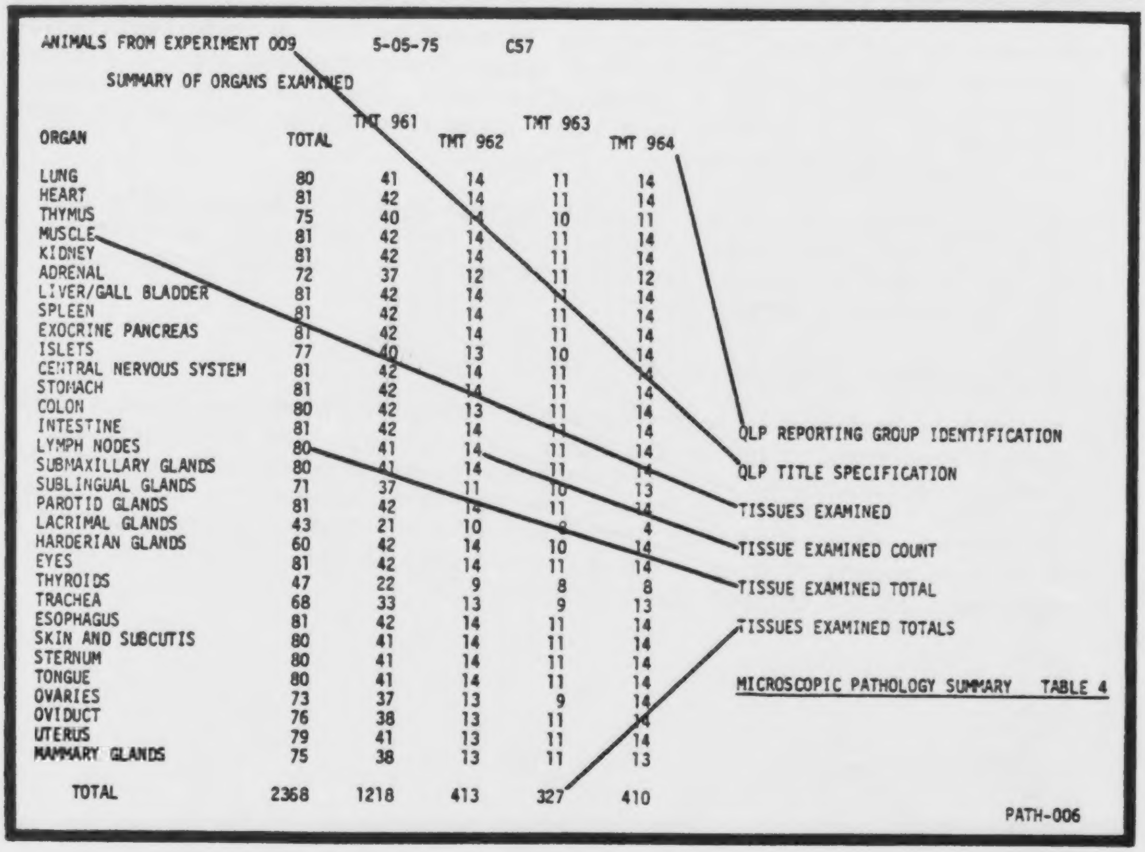
      NON-NEOPLASTIC PATHOLOGY SUMMARY BY GROUP      FEMALE

                                 TOTAL       TMT 961      TMT 962      TMT 963      TMT 964
LUNG
  LYMPHOCYTIC ACCUMULATIONS      8/  80      4/  41       1/  14       1/  11       2/  14
LUNG
  CRYSTALS                       1/  80      0/  41       0/  14       0/  11       1/  14
LUNG
  OTHER                          1/  80      0/  41       0/  14       0/  11       1/  14
HEART
  OTHER                          1/  81      1/  42       0/  14       0/  11       0/  14
THYMUS
  CYST                           2/  75      1/  40       0/  14       1/  10       0/  11
THYMUS
  OTHER                          1/  75      1/  40       0/  14       0/  10       0/  11
MUSCLE
  ACUTE INFLAMMATION             1/  81      0/  42       1/  14       0/  11       0/  14
MUSCLE
  CHRONIC INFLAMMATION           1/  81      0/  42       1/  14       0/  11       0/  14
KIDNEY
  HYDRONEPHROSIS                45/  81     26/  42      14/  14       3/  11       2/  14
KIDNEY
  PROTEINACEOUS CASTS           32/  81     20/  42       8/  14       2/  11       2/  14
KIDNEY
  PYELITIS                       8/  81      5/  42       2/  14
KIDNEY
  INFARCT                        1/  81      0/  42       1/  14
KIDNEY
  CALCIFICATION                  1/  81      1/  42       0/  14
KIDNEY
  CHRONIC INFLAMMATION          20/  81      9/  42       6/  14
KINDEY
  CYST                           8/  81      4/  42       1/  14
KIDNEY
  OTHER                          5/  81      4/  42       0/  14
LIVER/GALL BLADDER
  CRYSTALS                       2/  81      2/  42       0/  14
```

QLP REPORTING GROUP IDENTIFICATION
QLP TITLE SPECIFICATION
TISSUE AND ABNORMAL PATHOLOGY
POSITIVE FINDINGS/NUMBER·EXAMINED
TOTAL POSITIVE/TOTAL EXAMINED

MICROSCOPIC PATHOLOGY SUMMARY   TABLE 2

PATH-004



```
ANIMALS FROM EXPERIMENT 009       5-05-75      C57

      SUMMARY OF ORGANS EXAMINED

                                   TMT 961             TMT 963
ORGAN                     TOTAL             TMT 962            TMT 964

LUNG                        80       41       14        11       14
HEART                       81       42       14        11       14
THYMUS                      75       40       14        10       11
MUSCLE                      81       42       14        11       14
KIDNEY                      81       42       14        11       14
ADRENAL                     72       37       12        11       12
LIVER/GALL BLADDER          81       42       14        11       14
SPLEEN                      81       42       14        11       14
EXOCRINE PANCREAS           81       42       14        11       14
ISLETS                      77       40       13        10       14
CENTRAL NERVOUS SYSTEM      81       42       14        11       14
STOMACH                     81       42       14        11       14
COLON                       80       42       13        11       14
INTESTINE                   81       42       14        11       14
LYMPH NODES                 80       41       14        11       14
SUBMAXILLARY GLANDS         80       41       14        11       14
SUBLINGUAL GLANDS           71       37       11        10       13
PAROTID GLANDS              81       42       14        11       14
LACRIMAL GLANDS             43       21       10         8        4
HARDERIAN GLANDS            60       42       14        10       14
EYES                        81       42       14        11       14
THYROIDS                    47       22        9         8        8
TRACHEA                     68       33       13         9       13
ESOPHAGUS                   81       42       14        11       14
SKIN AND SUBCUTIS           80       41       14        11       14
STERNUM                     80       41       14        11       14
TONGUE                      80       41       14        11       14
OVARIES                     73       37       13         9       14
OVIDUCT                     76       38       13        11       14
UTERUS                      79       41       13        11       14
MAMMARY GLANDS              75       38       13        11       13

    TOTAL                 2368     1218      413       327      410
```

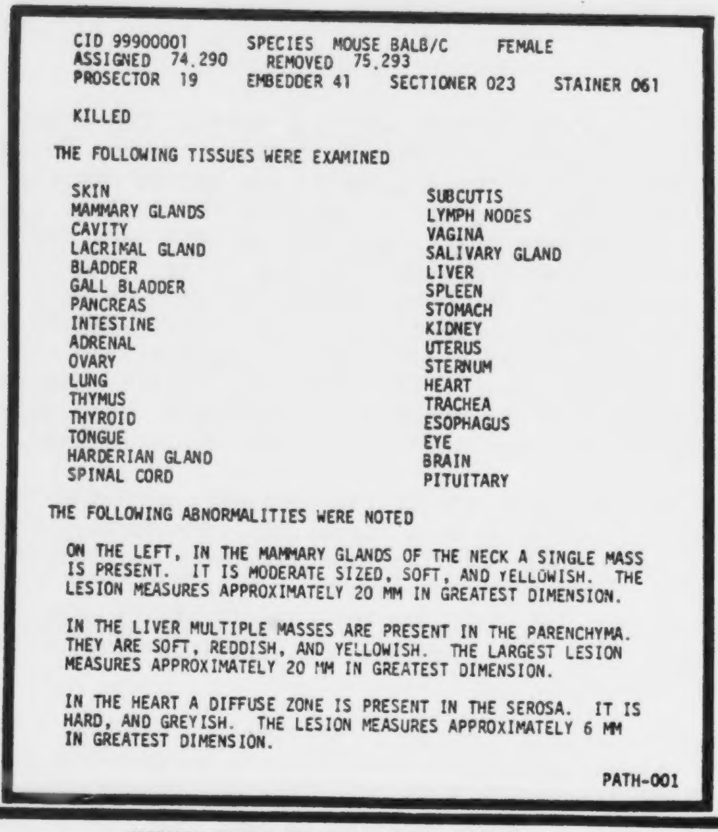
QLP REPORTING GROUP IDENTIFICATION
QLP TITLE SPECIFICATION
TISSUES EXAMINED
TISSUE EXAMINED COUNT
TISSUE EXAMINED TOTAL
TISSUES EXAMINED TOTALS

MICROSCOPIC PATHOLOGY SUMMARY   TABLE 4

PATH-006

FIGURE 4-20 (2)

Sample PEIS Reports



```
CID 99900001       SPECIES  MOUSE BALB/C      FEMALE
ASSIGNED  74.290     REMOVED  75.293
PROSECTOR  19      EMBEDDER 41     SECTIONER 023     STAINER 061

KILLED

THE FOLLOWING TISSUES WERE EXAMINED

  SKIN                                SUBCUTIS
  MAMMARY GLANDS                      LYMPH NODES
  CAVITY                              VAGINA
  LACRIMAL GLAND                      SALIVARY GLAND
  BLADDER                             LIVER
  GALL BLADDER                        SPLEEN
  PANCREAS                            STOMACH
  INTESTINE                           KIDNEY
  ADRENAL                             UTERUS
  OVARY                               STERNUM
  LUNG                                HEART
  THYMUS                              TRACHEA
  THYROID                             ESOPHAGUS
  TONGUE                              EYE
  HARDERIAN GLAND                     BRAIN
  SPINAL CORD                         PITUITARY

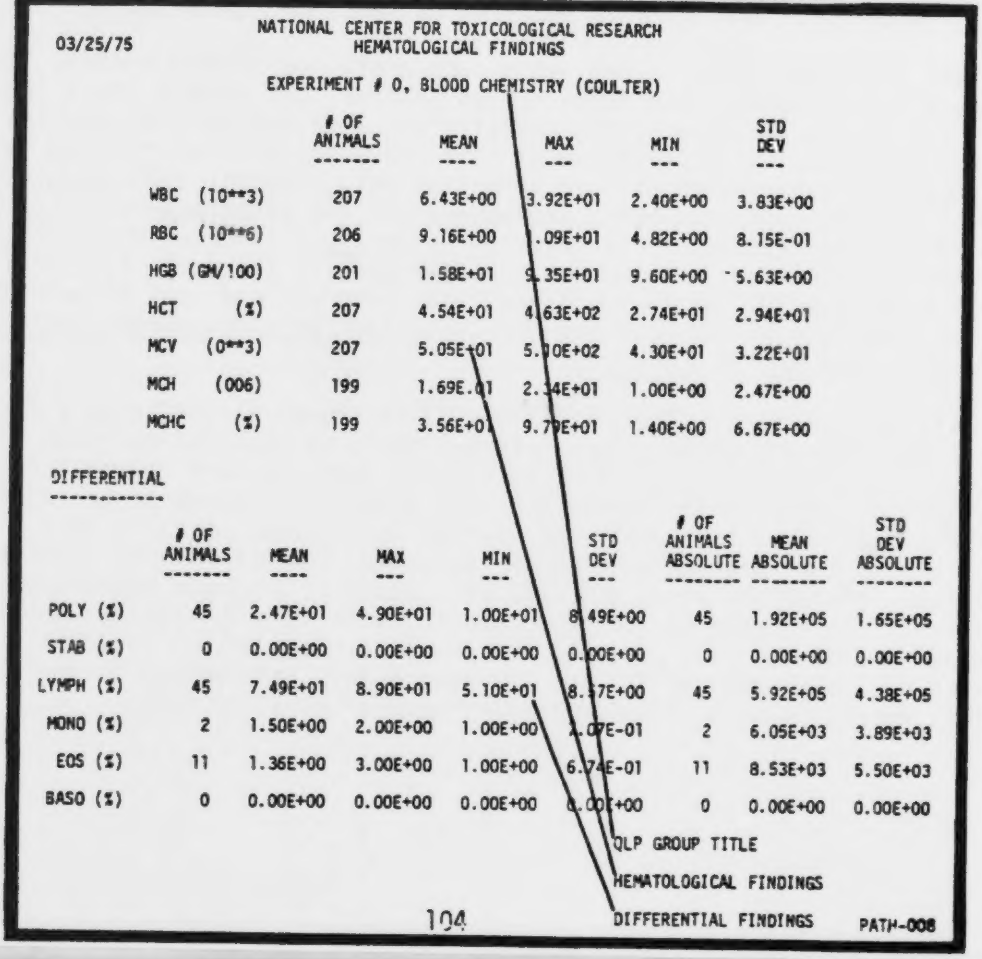
THE FOLLOWING ABNORMALITIES WERE NOTED

  ON THE LEFT, IN THE MAMMARY GLANDS OF THE NECK A SINGLE MASS
  IS PRESENT.  IT IS MODERATE SIZED, SOFT, AND YELLOWISH.  THE
  LESION MEASURES APPROXIMATELY 20 MM IN GREATEST DIMENSION.

  IN THE LIVER MULTIPLE MASSES ARE PRESENT IN THE PARENCHYMA.
  THEY ARE SOFT, REDDISH, AND YELLOWISH.  THE LARGEST LESION
  MEASURES APPROXIMATELY 20 MM IN GREATEST DIMENSION.

  IN THE HEART A DIFFUSE ZONE IS PRESENT IN THE SEROSA.  IT IS
  HARD, AND GREYISH.  THE LESION MEASURES APPROXIMATELY 6 MM
  IN GREATEST DIMENSION.

                                                        PATH-001
```



```
03/25/75              NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH
                                 HEMATOLOGICAL FINDINGS

                      EXPERIMENT # 0, BLOOD CHEMISTRY (COULTER)

                          # OF                                              STD
                        ANIMALS      MEAN         MAX          MIN          DEV
                        -------      ----         ---          ---          ---

          WBC  (10**3)    207      6.43E+00     3.92E+01     2.40E+00     3.83E+00

          RBC  (10**6)    206      9.16E+00     [illegible].09E+01     4.82E+00     8.15E-01

          HGB (GM/100)    201      1.58E+01     9.35E+01     9.60E+00    -5.63E+00

          HCT      (%)    207      4.54E+01     4.63E+02     2.74E+01     2.94E+01

          MCV   (0**3)    207      5.05E+01     5.[illegible]0E+02     4.30E+01     3.22E+01

          MCH    (006)    199      1.69E.01     2.[illegible]4E+01     1.00E+00     2.47E+00

          MCHC     (%)    199      3.56E+01     9.7[illegible]E+01     1.40E+00     6.67E+00

DIFFERENTIAL
------------
                                                                       # OF                    STD
               # OF                                          STD     ANIMALS      MEAN         DEV
             ANIMALS    MEAN       MAX        MIN            DEV     ABSOLUTE   ABSOLUTE    ABSOLUTE
             -------    ----       ---        ---            ---     --------   --------    --------

 POLY (%)       45    2.47E+01   4.90E+01   1.00E+01      8.49E+00      45      1.92E+05    1.65E+05

 STAB (%)        0    0.00E+00   0.00E+00   0.00E+00      0.00E+00       0      0.00E+00    0.00E+00

LYMPH (%)       45    7.49E+01   8.90E+01   5.10E+01      8.[illegible]7E+00      45      5.92E+05    4.38E+05

 MONO (%)        2    1.50E+00   2.00E+00   1.00E+00      [illegible].07E-01       2      6.05E+03    3.89E+03

  EOS (%)       11    1.36E+00   3.00E+00   1.00E+00      6.74E-01      11      8.53E+03    5.50E+03

 BASO (%)        0    0.00E+00   0.00E+00   0.00E+00      0.00E+00       0      0.00E+00    0.00E+00
```

PATH-008

There are two major components involved in a typical QLP search and retrieval session. The first component includes an inquiry command facility to select the desired information from the data base; the second component utilizes standard report formatting programs to generate the desired output. A command language is provided whereby users specify a generic name and associated value to select information from the TDMS data bases. The current QLP at NCTR is not useroriented in that the command language is very structured and not easy to use. Under current procedures, users specify their requirements to an information specialist who then interacts with the TDMS data base using a CRT display screen. The query results are received by the operator who sends them to the appropriate requestor. The improved QLP for the TDMS will provide for more direct involvement by the user.

A major goal of the QLP is to aid in the preparation of the final report for an experiment. To provide this capability, the summary report formats required for a final report, similar to the summary reports described in Appendix B of this report, will be specified and individual report generator programs developed. In this way the reports may be used for both final report preparation and independent analysis and evaluation using a variety of selection specifications.

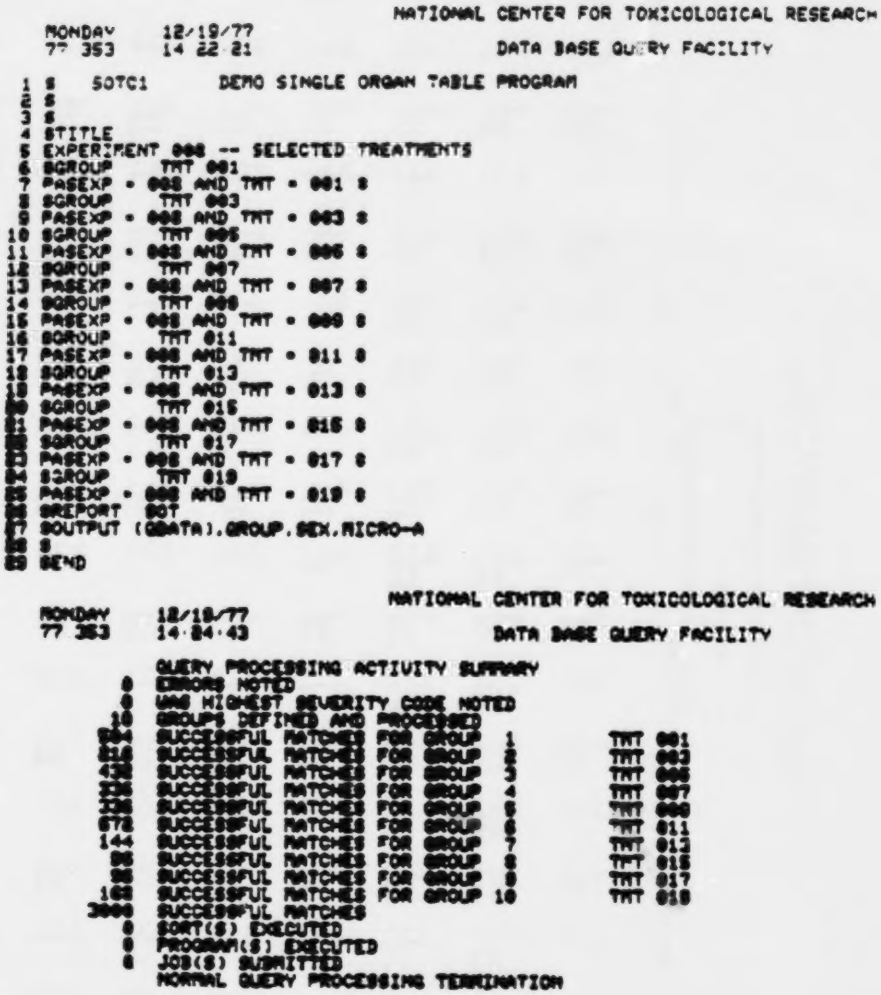
The QLP interfaces with the commercial statistical package. The results are returned to QLP and displayed on a CRT. To accommodate this graphic capability, QLP utilizes a TEKTRONIX 4014 display terminal and an associated hard copier. Part of a QLP session is shown in Figure 4-21.

The TDMS described above is not yet a completely operational system. Both NCTR and NCI currently have computerized systems that support their requirements and are replacing existing capabilities with various TDMS modules on an as needed basis. It is estimated that two years will be required to implement the entire TDMS at both organizations. The only TDMS module that is designed and currently being implemented is the pathology recording portion of the Post Experiment Information System. It is being developed at both NCTR and NCI and is scheduled for operation in the early part of 1979. Figure 4-22 is a 1977 estimate of the time, manpower and cost of developing the TDMS from an NCI/NCTR report, Toxicology Data Management System, Phase I Systems Analysis Report.

The data for the various TDMS modules will be stored according to a data base free structure which allows information to be recorded in varying levels of specificity, i.e., from very broad terms to very narrow terms. This type of organization allows new data elements or terms to be added to the overall structure with a minimum of difficulty, which is very important in a phased-implementation approach. The QLP will be able to integrate information among the TDMS data bases in a single query specification. The current Toxicology Support System at NCTR provides on-line storage for all the data recorded for every test conducted. As TDMS modules are developed, NCTR plans to convert this information to the TDMS format, resulting in no loss or obsolescence of existing data.

FIGURE 4-21 (1)

Sample QLP Terminal Session



```
                                  NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH
MONDAY     12/19/77
77 353     14 22 21                          DATA BASE QUERY FACILITY

$    SOTC1       DEMO SINGLE ORGAN TABLE PROGRAM
$
$
$TITLE
EXPERIMENT 008 -- SELECTED TREATMENTS
$GROUP      TMT 001
PASEXP = 008 AND TMT = 001 $
$GROUP      TMT 003
PASEXP = 008 AND TMT = 003 $
$GROUP      TMT 005
PASEXP = 008 AND TMT = 005 $
$GROUP      TMT 007
PASEXP = 008 AND TMT = 007 $
$GROUP      TMT 009
PASEXP = 008 AND TMT = 009 $
$GROUP      TMT 011
PASEXP = 008 AND TMT = 011 $
$GROUP      TMT 013
PASEXP = 008 AND TMT = 013 $
$GROUP      TMT 015
PASEXP = 008 AND TMT = 015 $
$GROUP      TMT 017
PASEXP = 008 AND TMT = 017 $
$GROUP      TMT 019
PASEXP = 008 AND TMT = 019 $
$REPORT  SOT
$OUTPUT (QDATA).GROUP.SEX.MICRO-A
$
$END
                                  NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH
MONDAY     12/19/77
77 353     14.24.43                          DATA BASE QUERY FACILITY

          QUERY PROCESSING ACTIVITY SUMMARY
       0  ERRORS NOTED
       0  WAS HIGHEST SEVERITY CODE NOTED
      10  GROUPS DEFINED AND PROCESSED
     504  SUCCESSFUL MATCHES FOR GROUP  1          TMT 001
     216  SUCCESSFUL MATCHES FOR GROUP  2          TMT 003
     432  SUCCESSFUL MATCHES FOR GROUP  3          TMT 005
     336  SUCCESSFUL MATCHES FOR GROUP  4          TMT 007
     336  SUCCESSFUL MATCHES FOR GROUP  5          TMT 009
     672  SUCCESSFUL MATCHES FOR GROUP  6          TMT 011
     144  SUCCESSFUL MATCHES FOR GROUP  7          TMT 013
      96  SUCCESSFUL MATCHES FOR GROUP  8          TMT 015
      96  SUCCESSFUL MATCHES FOR GROUP  9          TMT 017
     168  SUCCESSFUL MATCHES FOR GROUP 10          TMT 019
    3000  SUCCESSFUL MATCHES
       0  SORT(S) EXECUTED
       0  PROGRAM(S) EXECUTED
       0  JOB(S) SUBMITTED
          NORMAL QUERY PROCESSING TERMINATION
```

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FIGURE 4-21 (2)

Sample QLP Terminal Session

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```
                           NUMBER OF POSITIVES SINGLE ORGAN TABLE                              PAGE 1. 1
                               EXPERIMENT 008 -- SELECTED TREATMENTS

                                         ***************************
                                         *                         *
                                         *    BLADDER              *
                                         *                         *
                                         ***************************
              TOTALS      TMT 001             TMT 005            TMT 009             TMT 013             TMT 017
                                     TMT 003            TMT 007            TMT 011             TMT 015             TMT 019

AUTOLYSIS
  MALE          0/    1     0/   0    0/   0    0/   0    0/   0    0/   1    0/   0    0/   0    0/   0    0/   0    0/   0
  FEMALE      125/ 2962     3/ 498    7/ 818    4/ 432   18/ 334    0/ 332   70/ 663    3/ 137    0/  96    3/  96   16/ 183
  TOTAL       125/ 2963     3/ 498    7/ 818    4/ 432   18/ 334    0/ 333   70/ 663    3/ 137    0/  96    3/  96   16/ 183

VACUOLIZATION
  MALE          0/    1     0/   0    0/   0    0/   0    0/   0    0/   1    0/   0    0/   0    0/   0    0/   0    0/   0
  FEMALE     2180/ 2962   481/ 498  189/ 818  386/ 432  301/ 334  270/ 332  589/ 663    1/ 137    0/  96    4/  96    0/ 183
  TOTAL      2180/ 2963   481/ 498  189/ 818  386/ 432  301/ 334  270/ 333  589/ 663    1/ 137    0/  96    4/  96    0/ 183

HYPERPLASIA
  MALE          0/    1     0/   0    0/   0    0/   0    0/   0    0/   1    0/   0    0/   0    0/   0    0/   0    0/   0
  FEMALE     2081/ 2962   470/ 498  187/ 818  427/ 432  271/ 334  301/ 332  470/ 663    0/ 137    0/  96    0/  96    0/ 183
  TOTAL      2081/ 2963   470/ 498  187/ 818  427/ 432  271/ 334  301/ 333  470/ 663    0/ 137    0/  96    0/  96    0/ 183

SQUAMOUS METAPLASIA
  MALE          0/    1     0/   0    0/   0    0/   0    0/   0    0/   1    0/   0    0/   0    0/   0    0/   0    0/   0
  FEMALE       28/ 2962     3/ 498    3/ 818    1/ 432   16/ 334    1/ 332    4/ 663    0/ 137    0/  96    0/  96    0/ 183
  TOTAL        28/ 2963     3/ 498    3/ 818    1/ 432   16/ 334    1/ 333    4/ 663    0/ 137    0/  96    0/  96    0/ 183

DYSPLASIA
  MALE          0/    1     0/   0    0/   0    0/   0    0/   0    0/   1    0/   0    0/   0    0/   0    0/   0    0/   0
  FEMALE        1/ 2962     0/ 498    0/ 818    0/ 432    0/ 334    0/ 332    1/ 663    0/ 137    0/  96    0/  96    0/ 183
  TOTAL         1/ 2963     0/ 498    0/ 818    0/ 432    0/ 334    0/ 333    1/ 663    0/ 137    0/  96    0/  96    0/ 183

STROMAL INFILTRATION
  MALE          0/    1     0/   0    0/   0    0/   0    0/   0    0/   1    0/   0    0/   0    0/   0    0/   0    0/   0
  FEMALE       81/ 2962     0/ 498    0/ 818    1/ 432    4/ 334    0/ 332    0/ 663    0/ 137    0/  96    0/  96    1/ 183
  TOTAL        81/ 2963     0/ 498    0/ 818    1/ 432    4/ 334    0/ 333    0/ 663    0/ 137    0/  96    0/  96    1/ 183

FIBROSIS
  MALE          0/    1     0/   0    0/   0    0/   0    0/   0    0/   1    0/   0    0/   0    0/   0    0/   0    0/   0
  FEMALE        1/ 2962     0/ 498    0/ 818    0/ 432    0/ 334    0/ 332    1/ 663    0/ 137    0/  96    0/  96    0/ 183
  TOTAL         1/ 2963     0/ 498    0/ 818    0/ 432    0/ 334    0/ 333    1/ 663    0/ 137    0/  96    0/  96    0/ 183

NECROSIS
  MALE          0/    1     0/   0    0/   0    0/   0    0/   0    0/   1    0/   0    0/   0    0/   0    0/   0    0/   0
  FEMALE        0/ 2962     0/ 498    0/ 818    0/ 432    0/ 334    0/ 332    0/ 663    0/ 137    0/  96    0/  96    0/ 183
  TOTAL         0/ 2963     0/ 498    0/ 818    0/ 432    0/ 334    0/ 333    0/ 663    0/ 137    0/  96    0/  96    0/ 183

HEMORRHAGE
  MALE          0/    1     0/   0    0/   0    0/   0    0/   0    0/   1    0/   0    0/   0    0/   0    0/   0    0/   0
  FEMALE        3/ 2962     0/ 498    0/ 818    0/ 432    0/ 334    1/ 332    0/ 663    0/ 137    0/  96    0/  96    0/ 183
  TOTAL         3/ 2963     0/ 498    0/ 818    0/ 432    0/ 334    1/ 333    0/ 663    0/ 137    0/  96    0/  96    0/ 183

CALCIFICATION
  MALE          0/    1     0/   0    0/   0    0/   0    0/   0    0/   1    0/   0    0/   0    0/   0    0/   0    0/   0
  FEMALE        5/ 2962     0/ 498    1/ 818    0/ 432    1/ 334    0/ 332    3/ 663    0/ 137    0/  96    0/  96    0/ 183
  TOTAL         5/ 2963     0/ 498    1/ 818    0/ 432    1/ 334    0/ 333    3/ 663    0/ 137    0/  96    0/  96    0/ 183
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FIGURE 4-22

TDMS Implementation Schedule

	FY 77	FY 78												TOTAL	FY 79							
	S	O	N	D	J	F	M	A	M	J	J	A	S		O	N	D	J	F	M	A	M
		Initiate Hardware Procurement							Hardware Available										Trial			
Phase II - Design	10	10	11	12	12	12	12	12														
CMS	1	1	1	1	1	1	1	1														
ESS	2	2	2	2	2	2	2	2														
EIS	1	1	1	1	1	1	1	1														
PEIS	2	2	2	2	2	2	2	2														
QLP	2	2	2	2	2	2	2	2														
UTILITY FUNCTIONS	1	1	1	2	2	2	2	2														
LIASON	1	1	2	2	2	2	2	2														
Phase III - Development						1	2	3	14	14	15	15	15		15	15	15	14	14	14	14	11
CMS									1	1	1	1	1		1	1	1	1	1	1	1	1
ESS								1	3	3	3	3	3		3	3	3	3	3	3	3	2
EIS									2	2	2	2	2		2	2	2	2	2	2	2	1
PEIS									2	2	3	3	3		3	3	3	3	3	3	3	2
QLP							1	1	2	2	2	2	2		2	2	2	2	2	2	2	2
UTILITY FUNCTIONS						1	1	1	2	2	2	2	2		2	2	2	1	1	1	1	1
LIASON									2	2	2	2	2		2	2	2	2	2	2	2	2
Phase IV - Support & Maintenance																		2	2	2	3	3
Data Control																		1	1	1	1	1
Training																		1	1	1	2	2
Software Refinement																						
Manpower (MM)	10	10	11	12	12	13	14	15	14	14	15	15	15		15	15	15	16	16	16	17	14
Labor ($)	42	42	46.2	50.4	50.4	54.6	58.5	63	58.8	58.8	63	63	63		63	63	63	67.2	67.2	67.2	71.4	58.8
Travel (est. @ 8 trips/month avg.)	4	4	4	4	4	4	4	4	4	4	4	4	4		4	4	4	4	4	4	4	4
CPU	5	5	6	6	7	7	8	8	9	9	10	10	11		11	12	12	13	13	14	14	15
Total	51	51	56.2	60.4	61.4	65.6	70.8	75	71.8	71.8	77	77	78		78	79	79	84.2	84.2	85.2	89.4	77.8

TOTAL 1523.80

Dollar amounts are in thousands.

The data processing environment under which the TDMS will be operating is different for NCTR and NCI. At NCTR experiments are conducted, information is collected, and reports are generated at a single site. NCTR has its own central computer on-site (IBM 370/148). There are no long distance communications requirements and response time for reports and ad hoc requests is short. NCI relies on numerous subcontractors to conduct specified experiments and submit the results. NCI must monitor the status and progress of these subcontractors and evaluate the final results. Under TDMS operations, NCI will supply each contractor with the hardware required to collect and record experiment information in a standard format. The information collected locally will be transmitted to the NCI central computer at NIH/DCRT to update the master data bases. A network will be established for data transmission and QLP.

4.3.4 Evaluation of Existing Systems

There are a number of other existing, automated analytical capabilities (such as UPGRADE[1]) which could be interfaced with detailed test data for the purpose of conducting independent evaluations. What is unique about the TDMS, however, is its integration of virtually all the stated requirements of the CTSS. The only requirement not taken into account by TDMS is that pertaining to confidentiality, which is discussed further in Section 5.4.2. In addition, the TDMS is structured in such a manner so as to support an interface with other sources of data entry. NCTR has also expressed a willingness to provide conversion programs for machine-readable test data submitted from other testing laboratories.

Although TDMS maintains control animal data, it applies only to tests performed at NCTR. LADB, on the other hand, provides control animal data from several laboratory sources. If the detailed test data for the CTSS were defined in such a way as to consider the efforts of LADB and TDMS for the collection of control data, this would significantly reduce the transcription problem for the current LADB System and would make the analytical portions of both systems more compatible. Table 4-2 presents the summary of user requirements for CTSS which are met by TDMS and LADB.

1/ UPGRADE (User-Prompted GRAphic Data Evalution) is a software system for analyzing computerized data on the environment, natural resources, public health, and related topics.

Table 4-2

CTSS User Requirements Met by TDMS and LADB

CTSS User Requirements	Existing Systems	
Test Data Collection Standardization Monitoring	TDMS:	Compound Management System Protocol Analysis System Experiment Status System Experiment Information System Post Experiment Information System
Control Data	TDMS: LADB	Experiment Information System
Test Data Reporting Standardization Test Directory	TDMS:	Experiment Information System Post Experiment Information System Query Language Processor
Test Data Evaluation	TDMS:	Query Language Processor

The specification of a comprehensive detailed coding scheme for recording periodic observations and pathology findings and the acceptance of this scheme by participating laboratories is the single most difficult task in the development of data element specifications. An efficient coding scheme is necessary for comparing, correlating, and retrieving data in an automated system. Although a number of schemes have been developed to meet particular laboratory needs, there has been no overall consensus as to which system is best. Because of the variety of coding methods, transcription by laboratories into a single, standardized scheme requires considerable judgement and is thus prone to error.

Because SNOMED is designed with the human body and health care system in mind, the question arises whether it can accommodate the reporting requirements for laboratory animals. For instance, the topography field which identifies various parts of the human body does not have a code for a tail which is a part of the laboratory animals. Many laboratories have modified or extended with little difficulty the SNOP codes to meet their particular needs for coding animal tests. Certain laboratories that have implemented systems utilizing SNOP codes, such as the Primate Research Center (PRC), are cognizant of the benefits of the expanded and improved SNOMED codes, and are now in the process of adopting the new system. PRC indicated that the new SNOMED scheme covers additional terms not found in the modified SNOP system and the conversion of the modified SNOP codes to the SNOMED codes would not pose any significant problems.

Thus it seems that an expansion of SNOMED and/or a version of SNOP would prove the most viable basis for a coding scheme. However, the concern for preserving some free-text capability, especially in pathology, should be taken into account.

4.4 CSIN Systems Developments

Since June 1977 when the general design for a CSIN was first publicly aired, several efforts have been undertaken toward the realization of that concept. Many of the original assumptions and ideas concerning the network have been re-evaluated, reflecting the changes within the potential user community, particularly within the Office of Toxic Substances at EPA. This section intends to report the state-of-the-art of three key components of the CSIN which affect not only the CTSS but probably each other. Each of them is presently under development. In addition, several other possible components of CSIN which have some affinity with the CTSS are discussed.

4.4.1 Chemical Data Bases Directory (CDBD)

The Chemical Data Bases Directory, also referred to as the Chemical Information Resources Directory, will provide a subject classification of those data bases comprising the CSIN as well as a description of each data base in terms of its attributes (e.g., sponsor, method(s) of access, disseminator, kind of information it contains, etc.).

Two primary structures of the CDBD are the Descriptive Catalog and the Subject Catalog. The Descriptive Catalog specifies the name, description, functions, and format of each member of the CSIN; and the Subject used to build an extensive classification scheme and cross-reference system for matching the data elements of each CSIN component to the CDBD system vocabulary. The CDBD will serve to reference component data bases, but will not contain the specific data element values.

The Mitre Corporation is collecting the appropriate information for each data base and is building the file on WYLBUR at NIH. Twelve data bases have been selected for the prototype directory:

- Carcinogenesis Bioassay Data System (NCI)
- Chemical Formulations of Consumer Products (CPSC)

- Chemical Information System Substructure and Nomenclature System (EPA)
- CHEMLINE (NLM)
- Directory of Chemical Producers (Stanford Research Institute)
- Laboratory Animal Data Base (NLM)
  NIOSHTIC (NIOSH)
- Pesticide Products Information System (EPA)
- Poison Control Data Base (FDA)
- Registry of Toxic Effects of Chemical Substances (EPA, NIOSH, NLM)
- Toxicology Data Base (NLM)
- TOXLINE (NLM)

Every data base in the CSIN will be "registered" in the Directory.

4.4.2 Chemical Structure and Nomenclature System (CSNS)

The proposed CSNS will provide basic identification data for chemical substances which include molecular formula, chemical structure, CAS Registry Number, CAS preferred name, and synonyms. In addition to a sub-structure search capability, the CSNS will have a locator designator which will direct the user to the files in the CSIN which contain information on that particular chemical substance.

A contract was recently negotiated between CEQ and the University of Pennsylvania to conduct a study on the specific user requirements for the CSNS within the context of CSIN development. It is essential that the user communities be identified, that its needs be categorized in such a way as to indicate the difficult uses of the CSNS, and that existing chemical search systems such as the Chemical Information System (CIS) at EPA, be fully analyzed in terms of those specified user requirements.

4.4.3 Chemicals in Commerce Information System (CICIS)

Under a contract with Informatics, OTS is developing an information system to support the management and reporting requirements of TSCA. The general requirements of such a system include data for the TSCA Inventory (e.g. chemical identification, production information, manufacturer, geographic location); Premanufacture information (e.g., risk assessment, test standards and methodologics); and test results (e.g. assessment of health and environmental effects, monitoring and exposure studies).

It is apparent that there is some overlap between the kinds of information to be included in CICIS and in CTSS. Potential users who will be concerned with risk assessment and health and environmental effects will be interested in both acute and chronic studies, as was indicated in their discussions with Sigma Data. Given that CICIS is presently not planning to include an analytical capability but only a report mechanism for a test (i.e., bibliographic item), consideration might be given to directing test results, both raw data and summary reports, to the CTSS.

Similarly, because both current awareness and reported test results can be incorporated into and made available through existing systems, such as SSIE, NTIS, and/or TOXLINE, justification for capturing such data in CICIS as well needs to be developed.

In addition, it may be that use patterns will require that CICIS and CTSS be directly linked, however it is not within the scope of this report to make that determination. A contract has recently been let to the Computer Corporation of America to conduct a study of specific user needs and to formulate the appropriate network configuration. If there is to be a direct linkage, then the duplication of information in them would be difficult to justify.

4.4.4 Other Components

There are a number of other CSIN components which should be highlighted because of their potential relationship to the CTSS:

-RTECS: an on-line file which includes toxicity data for an estimated 2100 substances.

-LADB: see Section 4.3.2

-Toxicology Data Bank: a consolidated file of biological effects, e.g., acute toxicity, carcinogenicity, mutagenicity, teratogenicy, etc. on all types of chemicals. The estimated file size is 4000-5000 chemicals.

4.4.5 Conclusions

The configuration of CSIN is utlimately dependent upon the evolving needs of IRLG and other agencies. Some aspects will be better defined upon completion of the study conducted by the Computer Corporation of America. However, it is essential that further efforts towards the implementation of CTSS be cognizant of other CSIN component development.

In the interim, there are some steps which can be taken to maximize coordination among the components:

- use of the CAS Registry Number
- cooperation with CICIS to minimize areas of duplication and maximize logical and technological compatibility
- establishment of a link with LADB to enhance the collection of control animal data.

5.0 IMPLEMENTATION SCENARIO

5.1 Rationale for Implementation Scenario

The TDMS represents an integrated system for the collection and analysis of animal test data. Although it is not fully operational, there has been substantial effort expended by NCTR and NCI both in terms of conceptualization and of development. As an "existing", applicable system, every effort should be directed toward supporting and coordinating the development of the TDMS in order to incorporate the needs of the CTSS user community.

In selecting the TDMS for an implementation scenario, several factors were considered:

- Users - government agencies, particularly the IRLG would have easy access because the TDMS is a Federally-supported facility. It would be a significant step to permit private laboratories to have access to the analytical software as an incentive for complying with standardized data collection. In fact, NCI has already established automated source data entry with its contractors in the private sector.

- Technology - the TDMS supports the use of automated collection equipment with data transmission to the host computer daily. NCI has provided its laboratory contractors with minicomputers and floppy disks for source data entry. There is, therefore, a limited prototype network operation in progress.

- Costs - typically there is substantial cost in the development of software, especially of the analytical type required by a CTSS. Because NCTR has already developed the software, the remaining costs would include the purchase/lease of compatible, associated hardware, and the possible conversion from existing operations. However, NCTR has indicated an interest in assisting in the conversion process in order to promote standardization. Furthermore, significant savings could be effected if the cost for use of the analytical software were minimal.

- Impact on Existing Operations - this factor is closely related to the one above, particularly in the case of large, private laboratories which may have already invested in automated laboratory operations. However, as stated above, conversion programs can easily be written. A primary concern of OTS/EPA and FDA is the ability to "read" the tapes containing submitted test data. In order to implement effectively the TSCA reporting and testing requirements, it is essential for OTS to receive machine-readable data. The impact on data collection, both content and procedure, may be substantial, however, the resulting standardization may ease the reporting requirements on private industry as well as facilitate the evaluation process of government agencies.

- Confidentiality - there are numerous ways to build security mechanisms into computerized systems, ranging from physical security and encryption to complex user identification codes for the on-line files. To meet the needs of the NCI Carcinogenesis Bioassay Program, NCTR employs an operator ID and a password to gain access to data. Each data element is organized into a tree structure so that there are different levels of access available depending upon the identity of the user. NCTR has not reviewed confidentiality from the perspective of meeting TSCA requirements. This issue regarding proprietary data is, however, being addressed by EPA in their development of CICIS.

5.2 Proposed Development Plan

Each module of the TDMS is an independent entity which is an important advantage because it permits a phased implementation without entirely disrupting existing operations. There are two areas of development: data collection and data analysis. (For purposes of clarity, CTSS will be referred to as TDMS). A discussion of each follows:

5.2.1 Data Collection

Implementation of the TDMS is dependent upon the development and acceptance of standardized data submission and report formats as specified in the proposed design. The development of this "package" of data will essentially consist of defining detailed specifications for the worksheets identified in Appendix A, the machine-readable tape format, and the summary reports identified in Appendix B. These specifications shall be derived from the guidelines developed by the Testing Standards and Guidelines Workgroup as well as from Sections 4 and 5 of TSCA which have triggered the development of testing and reporting requirements.

Individual laboratories would have to ensure that the required data is gathered by their collection system, but the mechanism for gathering the data would be left up to each laboratory. Because existing collection systems do not entirely coincide with the standard detailed test data presented in Appendix A, laboratories will be confronted with a translation in order to conform to the standard reporting format, and to facilitate data access. Adoption of the TDMS data collection modules would eliminate the translation of test data however. As an added benefit, the information from the data collection modules could be used to generate the data submission "package" comprised of summary reports. On the other hand, NCTR could be responsible for supplying translation programs.

The cost of the associated hardware must be considered with the benefits of adopting the TDMS data collection modules. Many laboratories have sizable investments in automated data collection equipment and software. Incorporating the TDMS data collections modules would add to the cost of existing hardware. Figure 5-1 is an estimate of the hardware costs that would be incurred by a laboratory in order to implement the collection and reporting aspects of TDMS. These figures were obtained from the NCTR/NCI report prepared in September 1977 and entitled, *Toxicology Data Management System Phase 1 Systems Analysis Report*. The TDMS is not confined to automatic input, but under TSCA, the submission of data in compatible machine-readable form will be encouraged in order to facilitate test evaluation and analysis. Both OTE and NCTR have expressed interest in supporting the data reporting process through the development of tape conversion programs and in providing access to the TDMS analytical programs to generate summary reports.

Every attempt should be made to encourage laboratories with common collection requirements to enter into cooperative agreements to develop data collection systems that are compatible with the IRLG-GLP/TSCA guidelines. Data collection systems that are to be developed should use automated source data entry procedures as much as possible. This type of data gathering usually involves the interaction of laboratory personnel with a terminal or display screen that is connected on-line to a local or remote computer. There are several advantages to this type of system:

- Information is collected and entered immediately into the system at the source
- Data can be immediately edited before acceptance by the system
- Data not passing the edit criteria can be corrected at the source before transmission to the record
- Users can be prompted to insure that all required information is entered
- Historical data can be provided immediately in order to make comparisons
- The number of transfers and transcriptions of data is minimized

FIGURE 5-1

TDMS Data Collection Hardware Costs

18 Animal Rooms - 5 Active Stations

7 CRT Terminals (2 Back-up)	$35,000.00
7 Electronic Balances (2 Back-up)	17,500.00
7 Character Printers (2 Back-up)	7,000.00
3 Micro Computer/Disk Units	30,000.00
Total	$89,500.00

Microscopic Pathology - 2 Stations

2 CRT Terminals	$10,000.00
2 Character Printers	2,000.00
1 Micro Computer/Disk Unit	10,000.00
Total	$22,000.00

Administrative/PAS/ESS

1 CRT Terminal	$ 5,000.00
1 Line Printer	5,000.00
1 Micro Computer/Disk Unit	10,000.00
Total	$20,000.00
Total/Site	$131,500.00

There are two major disadvantages of on-line source data entry: the expense and effort involved in implementing the computer hardware; and the related software costs which are generally greater than a batch or manual type system. However, this added cost could be justified if accurate, timely data were collected, if data reporting requirements were facilitated.

5.2.2 Data Analysis

The TDMS, although only partially developed, is a flexible, open-ended hierarchical data base structure. It is designed for a time-phased implementation approach where changing or adding data element requirements can easily be incorporated into the system. Under the current implementation scheme, identical versions of the TDMS will be operational at NCTR which has its own computer facility, and at NCI which will utilize the NIH/DCRT computer facility. It is conceivable that one of these two facilities could act as the organizational entity to supervise an expanded TDMS to accommodate the requirements of the IRLG agencies, as well as other users. The information on completed tests would be stored off-line on tape and only transformed to on-line when needed. The additional disk storage required would not be significant since the NCTR system currently provides on-line storage for all animal experiments conducted at that organization. Since each experiment normally involves over 1000 animals, no more than two IBM dual density 3330 disk packs are required to store that test data.

By establishing compatible structures between active (on-line) and historical (off-line) files, a single TDMS Query Language Processor (QLP) could be used for access. The QLP used at NCTR to access the current data base will have to be modified to support the new TDMS data base and this has already been planned over a two year period. Although the QLP will be re-written, it will be based on the best features, capabilities, and operational experience of the current system. The QLP will not only provide the capability of comparing every data element associated with a particular test, but will also facilitate the comparison of data among multiple experiments. The QLP will be capable of producing a set of predefined reports such as those described in Appendix B. The new QLP should employ more user-oriented techniques and not rely on the services of an information specialist.

5.2.3 Systems Considerations

The two facilities, NCTR and NIH/DCRT are planning to provide an operational TDMS with a network communications capability. The NCTR facility is presently a node in the Public Health Service (PHS) Network and the NIH/DCRT facility used by NCI currently provides a network capability to many Federal agencies.

In orde to meet the needs of an expanded user community in both the public nd private sectors, network communications must be sufficiently develop d. Further steps in the development of CSIN must also be monitored and coo dinated wherever possible.

Because both NCTR and NCI already have the manpower to support the TDMS, the add tional manpower to support an enhanced system should be minimal. It can e expected that any added personnel could be for user support service .

5.2.4 Systems Options

Within he framework of the implementation scenairo discussed above, there are som options which are briefly delineated below:

- EPA, among others, has asserted the possibility of including non-laboratory animal studies and environmental studies. This could be easily integrated into the TDMS as long as standardization for the test data were in effect. The types of statistical analysis necessary for evaluation have broader application than just animal data.
- The development of CICIS at EPA may result in some overlap with the TDMS. (See Section 4.4.3). As stated earlier, the results of the study by the Computer Corporation of America on user requirements for CSIN should dictate the degree of allowable overlap, if any; the separation of certain types of data between the two systems; or if they should be directly linked via CSIN. Because the scope of CICIS has not been clarified to date, another option might be incorporating the Directory of Tests into CICIS. Implementation of the TDMS should consider concurrent and future developments with respect to the CSIN.
- Rather than establishing a separate Directory of Tests as a catalog to the Analysis File, it might be more useful to build a separate file within the TDMS which would consist of a catalog to the test data resident in the TDMS. In this way, a user could enter the TDMS data base, specify a chemical substance and a certain test (or whatever other data elements defined as searchable) to determine if such data existed, and if so, could then invoke the Analysis File.
- EPA might be asked to run the TDMS on their in-house computer facility. It does not seem necessary that one computer be designated as the sole central processing facility. Rather, it may be more cost effective to maintain distributed data bases each having TDMS analytical software. At the same time, the distributed data bases should be compatible to permit users to conduct easily searches/retrieval on each of them.

5.3 Time-Phase Implementation

Figure 5-2 illustrates a possible implementation plan developed by Sigma Data. Each task is identified with a start and end date, and the level of effort expressed in man-months. In appropriate cases, the number of man-months consists of the additional effort, beyond current or planned endeavors, to implement CTSS requirements. For instance, a TDMS data base structure is currently being developed at NCTR and NCI. The level of effort required for this task includes the additional man-months needed to incorporate the CTSS into the TDMS data base structure. The time-phasing in Figure 5-2 coincides with current plans or existing operations.

Once the IRLG guidelines have been approved and Sections 4 and 5 of TSCA pertaining to testing and reporting requirements have been further refined, the CTSS/TDMS specifications for detailed test data submission and summary reports can be developed. Animal experiments can be conducted according to standards as early as mid 1979; however, this will depend upon whether the existing, automated data collection systems of laboratories could adapt, or whether tape conversion programs could be written in that time period.

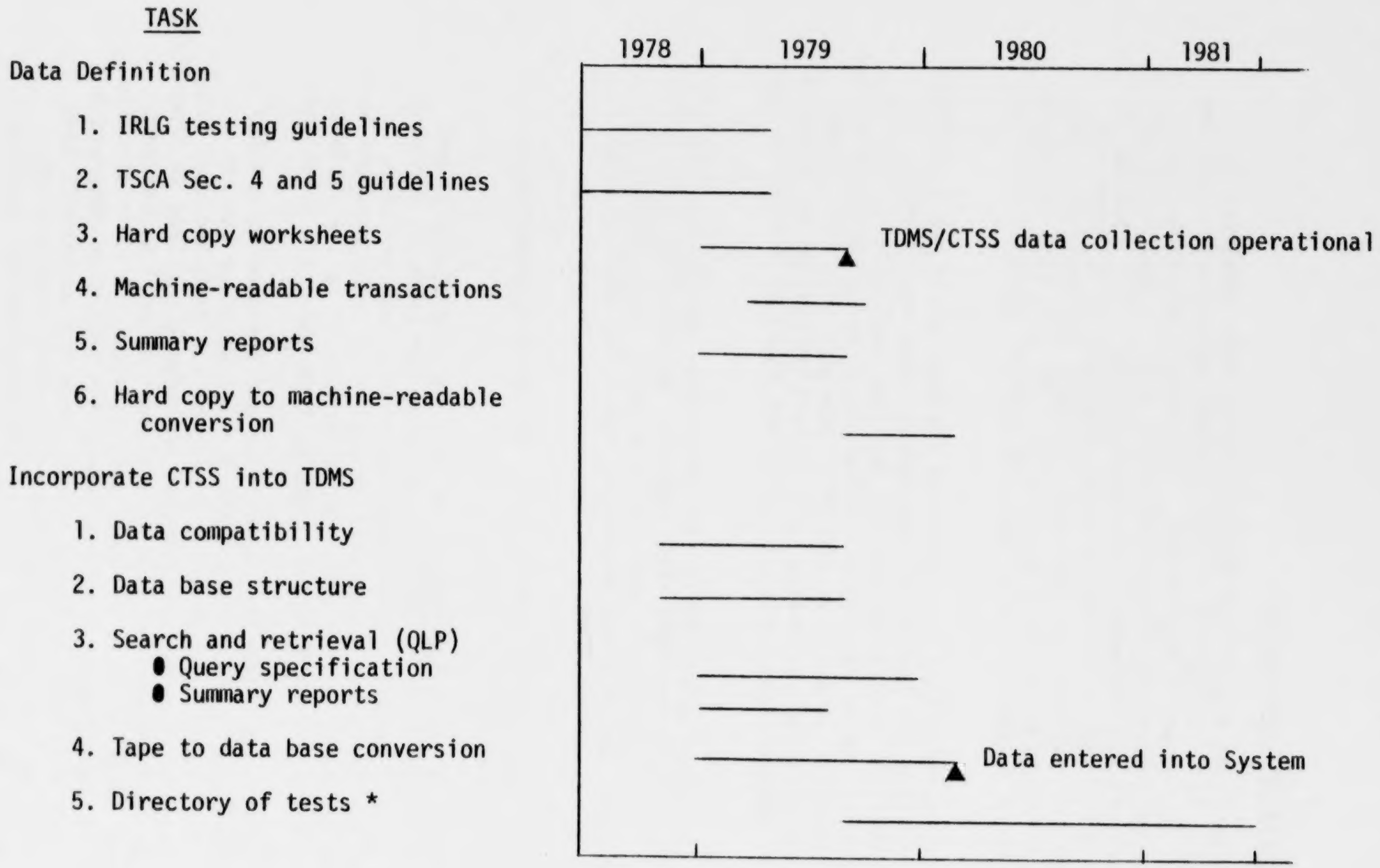
Laboratories utilizing manual collection procedures would have less of a problem conforming to the TDMS requirements. By mid-1980, detailed test data could be entered into the CTSS data base. By mid-1981, an on-line interactive analysis and evalution capability could be available for general use of the TDMS.

Data Definition - Responsible parties will have to be designated to implement the tasks enumerated below:

1. Initial IRLG Testing Guidelines - The IRLG Testing Standards and Guidelines Workgroup is currently developing requirements for nine types of tests. Guidelines for acute tests are now available. Guidelines for the other tests will be published throughout the next few months of 1979. Sufficient information should be available to design the worksheets and summary reports from the draft guidelines.

2. Hardcopy Worksheets - The IRLG guidelines and the Good Laboratory Practices and the TSCA Sections 4 and 5 rules would be used as a basis for the identification and grouping of the detailed test data elements required for the preformatted worksheets outlined in Appendix A. The standard format for each data element as well as standard descriptive codes for data elements such as route of administration will need to be defined. A coding scheme for recording observations and pathology will have to be approved. Once the worksheets have been approved by government agencies and testing laboratories, animal studies conducted according to TDMS requirements could be initiated.

Figure 5-2 CTSS/TDMS Time-Phase Implementation Plan



* Requires resolution of overlap with CICIS

3. Machine-readable Transactions - Using the hardcopy worksheets as a starting point, a comparable format for the machine-readable transactions used to submit detailed test data on magnetic tape will be defined. This includes the format of the transaction specification tables which consist of data element identifiers, length attributes and descriptors (Section 3.3.2).

4. Summary Reports - The design specifications of the summary reports outlined in Appendix B will be developed. The format for each report will be specified including a description of computations, sorts, translations, tabulations, procedures, etc., required to produce the document. The detailed test data used to produce each report will also be identified.

5. Hardcopy to Machine-Readable Conversion - a generalized software utility will be developed to convert test data submitted in hardcopy format to the machine-readable tape format for input to the on-line Analysis File. An automated key-to-tape system could provide the necessary support.

Incorporation of CTSS Requirements into TDMS

1. Data Compatibility - Because a portion of the TDMS is already designed, differences between CTSS and TDMS data elements will have to be resolved. This would include the coding scheme for pathology findings and physical and behavioral observations. This task will continue as additional testing guidelines are specified by the IRLG.

2. Data Base Structure - A data base structure will be needed to permit access to tests in progress and completed studies. Off-line and online files should be supported.

3. Search and Retrieval (QLP) - Query specifications techniques will be oriented to users not familiar with on-line interactive access to computer files. Software will be developed to present versions of the summary reports, outlined in Appendix A, on a computer display terminal. This task will coincide with current NCTR/NCI efforts.

4. Tape to Data Base Conversion - A computer utility will be developed to convert the detailed test data submitted on magnetic tape into the on-line storage format for the Analysis File. A computer utility will also be developed to convert completed tests stored on the TDMS data base into a historical format for the analysis file.

5. Catalog of CTSS Tests - A facility will be developed to store a list of all animal studies registered and available for investigation in a library or Directory. The list will be available to users in an on-line mode and should be registered with the Chemical Structure/Nomenclature System of the Chemical Substances Information Network in order to provide a referral linkage. Presumably these tests will also be reported to and cited by SSIE and NTIS where appropriate.

6. Network Development and User Testing - Communications requirements to support the users may be developed at NCTR or NIH/DCRT or at any other designated facility. The CTSS Analysis File should be available initially to a small number of users in order to evaluate the effectiveness of the system and make any necessary modifications or changes. At the end of this task, the Analysis File should be available for general use.

7. TDMS Data Collection Modules - The PEIS, EIS, and NADS modules of the TDMS will be modified and/or enhanced to be compatible with CTSS requirements. These automated data collection modules would be available to any testing laboratory desiring to adopt this data gathering procedure.

5.4 Development Implications

It has been two years since the Toxic Substances Control Act (TSCA) was signed into law, and nearly a year and a half since the publication of the Mitre report. Since that time, a number of steps have been taken toward meeting the information requirements which were explicit as well as implicit in TSCA. Furthermore, the initial framework for CSIN has been modified as the Office of Toxic Substances (OTS) became operational and as immediate information needs began to be identified. In order to focus upon the TDMS in a broader context, this section addresses its impact on TSCA and the issue of confidentiality, and its relevance to the CSIN.

5.4.1 Toxic Substances Control Act (TSCA)

The testing and reporting requirements of TSCA have been described by optimists as comprehensive, and by polite cynics, as gruesome. It places burdens on EPA for the review and evaluation of submitted studies in a relatively short period of time, and on private industry for its responsibility to report health and safety studies rapidly, to submit premanufacturing test results, and to supply sufficient data to support risk and hazard assessments for health and the environment.

The TDMS is designed to meet these tasks through the use of standardized data collection and reporting, and by computerized analytical techniques. The objectives are to upgrade the quality of test data, and to assist private laboratories in complying with TSCA and other laws, and to facilitate Federal agency regulatory activities.

5.4.2 Confidentiality

Since a portion of the test data submitted to Federal agencies, and therefore to the TDMS, will be proprietary, measures must be taken to ensure security. To a large extent, the decisions made with respect to proprietary data in CICIS should probably govern inclusion of and access to proprietary data in the TDMS.

Whatever the decision, it may play a role in the TDMS data base organization. For example, one method of securing data is to lock it up in a single physical location which maximizes the control over it. In terms of the TDMS, the result might be a series of distributed storage and analysis facilities, as well as one central, public facility.

5.4.3 Chemical Substances Information Network (CSIN)

As a core component of the CSIN, the implementation of the TDMS should attempt to be as compatible as possible, without violating its own mission, with other designated core components. The communications network selected for the full-scale TDMS implementation should also coordinate with CSIN. As discussed in Section 4.4, there are other systems, both planned and operational, which bear directly on the optimal use of TDMS.

5.5 Summary of Recommendations

The complete implementation of the TDMS will require at least two years; however, if the coordination and cooperation among Federal agencies is unconditional, then the TDMS may be realized earlier. The following recommendations are submitted with that objective in mind:

- development of work sheets and machine-readable formats for the IRLG Testing Standards and Guidelines and the TSCA Sections 4 and 5 rules.

- designation of a contractor to develop the hard-copy worksheets and machine-readable formats and to write the necessary tape conversion programs.

- coordination of efforts with personnel from NCI/NCTR.

- consultation and coordination with other groups within the regulatory agencies who are working on guidelines, such as the EPA/OTS Oncogenicity Group.

- establishment of a formal relationship with LADB for the exchange of control animal data.
- use of CAS Registry Number.
- development or refinement of a coding scheme for physical and pathology observations.
- inclusion of acute toxicity studies.
- consideration for the inclusion of environmental effects studies.
- strong coordination with CSIN development efforts.

APPENDIX A

PROTOTYPE CTSS HARDCOPY WORKSHEETS

APPENDIX A

01 - EXPERIMENT IDENTIFICATION

Laboratory performing test:

- Name
- Address

Internal experiment number

Date test was started

Date test ended

Type of experiment (acute dermal, teratogenicity, etc.)

Species

Principal person responsible for test

Contact person for additional information:

- Name
- Phone number

Test Substance(s):

- Chemical name(s)
- CAS registry number
- Trade name(s)

APPENDIX A

02 - SUMMARY AND CONCLUSIONS

In narrative form:

- Summary of the data collected
- Analysis of the data
- Statement of the conclusions
- Name of the person(s) responsible for completing the narrative

APPENDIX A

03 - TEST SUBSTANCE BATCH DATA

Batch Number

CAS Registry Number

EPA Inventory Number

Chemical name

Name of manufacturer

Lot and sample number(s)

Purity of batch

Physical state of batch

Critical termperature range

Date received from supplier

Date of manufacture

Original storage by supplier

Methods of preparation or synthesis

Special treatment applied after receipt

Chemical assays

Comments

APPENDIX A

04 - TEST SUBSTANCE PREPARATION DATA

Preparation number

Composition:

CAS #	Chemical Name	Batch Number	Concentration	Unit of Measure
______	___________	__________	___________	_____________
______	___________	__________	___________	_____________
______	___________	__________	___________	_____________

How often prepared

Date prepared

Mode of storage

Stability

PH

Particle size (inhalation):

- Mass diameter
- Count diameter
- Method used to determine size

State of preparation (granule, powder, particle, etc.)

Comments

APPENDIX A

05 - COLONY DATA

Species

Strain

Groups in which animals are used (range of group identification codes)

Source of animal supply

Disease control

Historical data on normal life span (i.e., LADB)

APPENDIX A

06 - ANIMAL GROUP DATA

Group identification code

Animal identification code:

- Low
- High

Number of animals in the group

Set of animals (male, female, other)

Median age

Range of ages

Median weight

Range of weights

Group role (test, vehicle control, untreated control, etc.)

Method of selection

Special treatment (surgery, diet change, etc.)

Pretest conditioning

Selection rationale

APPENDIX A

07 - DOSE REGIMEN

Group Identification Code

Dosages:

Preparation Number	Date of First Dose	Average Age At First Dose	Route of Administration	Amount of Preparation	Frequency of Dosage	Duration of Dosage

APPENDIX A

08 - LABORATORY PERSONNEL DATA

Identification Code	Name	Job Description

APPENDIX A

09 - INDIVIDUAL ANIMAL OBSERVATION

Group identification code

Animal identification code

Observation date:

- Month, day, year
- Hour, minute

Person making observation:

- Identification code
- Signature

Weight of animal

Food consumed

Cage conditions

Disposition (scheduled sacrifice, moribund, missing, dead, etc.)

Clinical signs:

- Predefined coded descriptions
- Free-text of non-standard situations

APPENDIX A

10 - INDIVIDUAL ANIMAL GROSS NECROPSY

Group identification code

Animal identification code

Date conducted:

- Month, day, year
- Hour, minute

Person conducting exam:

- Identification code
- Signature

Date of death:

- Month, day, year
- Hour, minute

Weight at death

Age at death

Disposition (sacrifice, natural death, etc.)

Condition of animal (fresh, cannibalized, etc.)

Results:

Organ Examined	Predefined Coded Findings	Free-Text Description of Findings	Number of Abnormalities or Lesions	Measurement	Grading
______	________	_________	___________	_________	_____
______	________	_________	___________	_________	_____
______	________	_________	___________	_________	_____
______	________	_________	___________	_________	_____

APPENDIX A

11 - INDIVIDUAL ANIMAL HISTOPATHOLOGICAL EXAMINATION

Group identification code

Animal identification code

Date conducted:

- Month, day, year
- Hour, minute

Person conducting examination:

- Identification code
- Signature

Results:

Organ Examined	Coded Findings	Free-Text Description of Findings	Caused Death (Y,N)	Caused Moribundity (Y,N)
______	______	________	____	________
______	______	________	____	________
______	______	________	____	________
______	______	________	____	________

APPENDIX A

12 - ORGAN WEIGHTS

Group identification code

Animal identification code

Date weighed:

- Month, day, year
- Hour, minute

Person weighing animal:

- Identification code
- Signature

Body weight

Individual Organs:

Organ Weighed	Weight
____	____
____	____
____	____
____	____
	____

APPENDIX A

13 - HEMATOLOGY ANALYSIS

Group identification code

Animal identification code

Date conducted:

- Month, day, year
- Hour, minute

Person conducting test:

- Identification code
- Signature

Hematocrit

Hemaglobin

Erythrocyte

Total leucocyte count

Differential leucocyte count

Reticulocyte count

Comments

APPENDIX A

14 - BLOOD CHEMISTRY ANALYSIS

Group identification code
Animal identification code
Date conducted:
  - Month, day, year
  - Hour, minute

Person conducting test:
  - Identification code
  - Signature

Fasting glucose
Blood urea nitrogen
Total protein
Hepatic enzymes
Carbohydrate metabolism
Liver function (SPGT, SCOT, SAP)
Kidney function
Electrolytes
Lipids
Hormones
Blood cretinine
Lactic dehydroginase
Direct bilirubin
Total bilirubin
Albumin
Calcium
Phosphorous
Chloride
Sodium
Potassium
Comments

APPENDIX A

15 - RESIDUE ANALYSIS

Group identification code

Animal identification code

Data conducted:

- Month, day, year
- Hour, minute

Person conducting test:

- Identification code
- Signature

Results:

- Blood
- Fat
- Liver
- Kidney

Comments

APPENDIX A

16 - CHOLINESTERASE ANALYSIS

Group identification code

Animal identification code

Date conducted:

- Month, day, year
- Hour, minute

Person conducting test:

- Identification code
- Signature

Results:

- Acetyl cholinesterase
- Non-specific esterase in red blood cells

Comments

APPENDIX A

17 - URINALYSIS RESULTS

Group identification code

Animal identification code

Date conducted:

- Month, day, year
- Hour, minute

Person conducting test:

- Identification number
- Signature

Results:

- PH
- Specific gravity
- Sugar
- Ketones
- Protein
- Bilirubin
- Sediment
- Stone analysis (if observed)
- Residues and metabolites

Comments

APPENDIX A

18 - INDIVIDUAL ANIMAL DISEASE AND TREATMENT

Group identification code

Animal identification code

Nature and severity of disease

Date of first observation (month, day, year)

Duration of disease

Nature of any treatment(s)

Date(s) of such treatment(s)

Outcome of disease

APPENDIX A

19 - ENVIRONMENTAL MONITORING

Group identification code(s): (may be a range of codes)

- Low
- High

Humidity range (high, low)

Temperature range (high, low)

Number of changes per hour of room air

Room air filtration

Communication between animal rooms (open, partial, none, etc.)

Exposure to light (hour/day):

- Natural
- Tungsten
- Flourescent
- Ultraviolet

Recordings:

Month, Day, Year	Hour, Minute	Temperature	Humidity
____________	________	________	_____
____________	________	________	_____
____________	________	________	_____
____________	________	________	_____
____________	________	________	_____

APPENDIX A

20 - ANIMAL FEED AND WATER DATA

Group identification code(s): (may be a range of codes)

- Low
- High

Name of feed
Name of feed manufacturer
Name of feed supplier
Analysis of feed
Feed consumption (ad lib, measured, etc.)
Form of feed (pellet, powder, etc.)
How feed is given (cage lid, separate pan, hopper, etc.)
Water source (tap, distilled, etc.)
Water distribution (glass bottle, plastic bottle, etc.)
Water consumption (ad lib, measured, etc.)
Chlorine content of water
Flouride content of water
Analysis of water
Additives in water

APPENDIX A

21 - Animal Bedding Data

Group identification code(s): (may be a range of groups)

- Low
- High

Commercial name of bedding

Name of bedding manufacturer

Type of bedding material (wood chips, shovings, etc.)

Sterilization of bedding

Comments

APPENDIX A

22 - ANIMAL CAGE DATA

Group identification code(s): (may be a range of codes)

- Low
- High

Cage dimensions

Number of cages per 100 sq. ft. of floor space

Cage manufacturer

Cage material (metal, polypropylene, etc.)

Cage construction (solid, perforated, etc.)

Cage sanitation

APPENDIX A

23 - EQUIPMENT MAINTENANCE

Equipment identification

Date conducted:

- Month, day, year
- Hour, minute

Person performing maintenance:

- Identification code
- Signature

Description of maintenance and cleaning

Description of calibration

Inspection results

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Animal Group Profile

TESTS: All Tests

Group Identification	Group Role	Selection Method	Animal Age		Animal Weight		Total Number of Animals	Animal Identification		Sex
			Avg.	Std.dev.	Avg.	Std.dev.		Low	High	
______	___	____	__	___	__	____	_____	__	___	__
								__	___	__
								__	___	__

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Dose Levels by Test Group

TESTS: All Tests

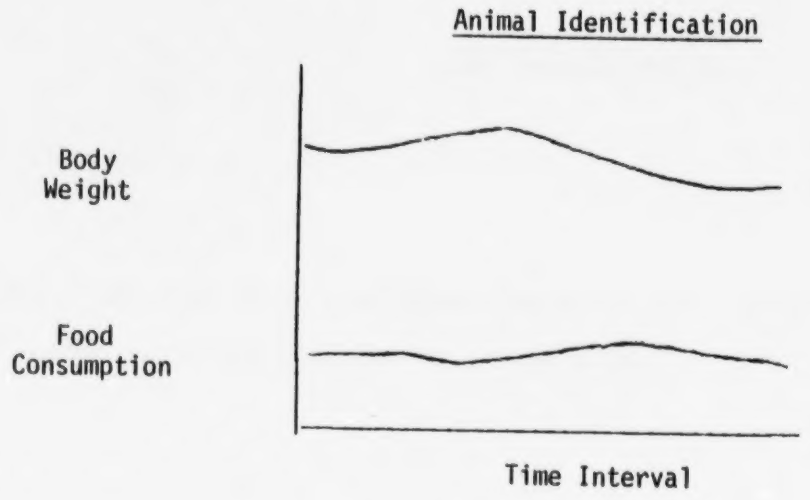
Group Identification	Test Substance		Administration			Date First Administered	Average Age of Animals at First Administration
	Amount	Preparation Number	Frequency	Duration	Route		
___	___	___	___	___	___	___	___
	___	___	___	___	___	___	___
	___	___	___	___	___	___	___

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Weight Change and Food Consumption by Individual Animal

TESTS: Acute Dermal, Acute Inhalation, Acute Oral, Subchronic Dermal, Subchronic Inhalation, Subchronic Oral, Reproduction

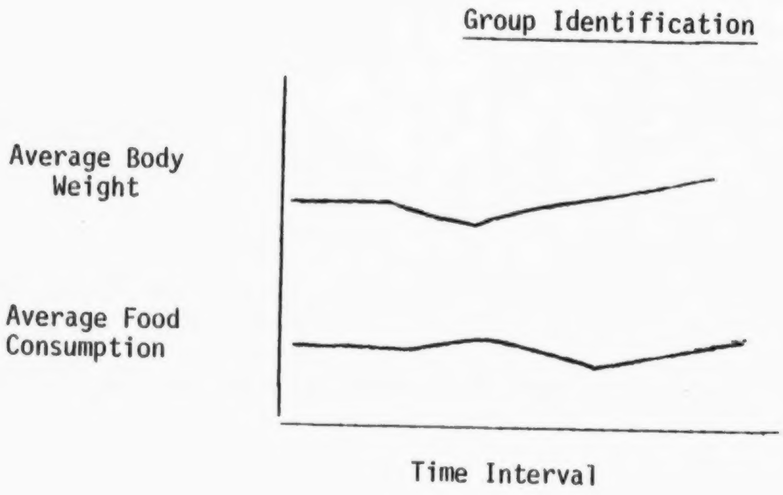


APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Average Weight Change and Food Consumption by Group

TESTS: Acute Inhalation, Subchronic Inhalation, Subchronic Oral, Reproduction



APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Record of Physical/Behavioral Observations by Individual Animal

TESTS: All Tests

Group Identification	Animal Identification	Observation			
		Date	Time	Duration	Description
________	________	__	__	_____	_______
		__	__	_____	_______
		__	__	_____	_______
	________	__	__	_____	_______
		__	__	_____	_______

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Summary of Clinical Signs by Test Group

TESTS: Subchronic Oral

Test Group
Number of Animals in Group

Clinical Signs	Animals Showing Effect	Time From Start of Test to First Observation	Age at Death of Animals Not Sacrificed
______	______	______	______
______	______	______	______
______	______	______	______

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Incidence of Physical/Behavioral Observations by Test Group

TESTS: Acute Inhalation, Acute Ocular, Acute Oral, Reproduction

Test Group / Observation	Group # 1		Group # 2		Group # 3	
	No.	%	No.	%	No.	%
Observation # 1*	___	___	___	___	___	___
Observation # 2	___	___	___	___	___	___
Observation # 3	___	___	___	___	___	___

* e.g. Palpable Tumor

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Gross Necropsy Examination for an Individual Animal

TESTS: Acute Dermal, Acute Inhalation, Acute Oral, Subchronic Dermal, Subchronic Inhalation, Subchronic Oral, Teratogenicity, Reproduction

Dose Group
Animal Identification

Organ or Tissue Examined	Diagnosis of Gross Abnormality	Data First Observed	Measurement	Grading
________	________	____	______	
________	________		______	____
________	________	____		____

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Summary of Gross Necropsy Examination by Test Group

TESTS: Subchronic Inhalation, Subchronic Oral, Reproduction

Test Group Gross Abnormality	Group # 1	Group # 2	Group # 3
Abnormality #1 *	no./tot.	no./tot.	no./tot.
Abnormality #2	no./tot.	no./tot.	no./tot.
Abnormality #3	no./tot.	no./tot.	no./tot.

* e.g. Large Liver Lesions

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Histological Examination for an Individual Animal

TESTS: Acute Dermal, Acute Inhalation, Acute Oral, Subchronic Dermal, Subchronic Inhalation, Subchronic Oral, Teratogenicity, Reproduction

Dose Group
Animal Identification

Organ or Tissue Examined	Diagnosis and Characterization	Number of Lesions or Tumors	Date First Observed	Caused Death (y,n)	Caused Moribundity (y,n)
________	________	______	_____	__	______
________	________	______	_____	__	______
________	________	______	_____	__	______

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Summary of Histopathological Findings by Test Group

TESTS: Subchronic Inhalation, Subchronic Oral

Test Group Histopathological Finding	Group # 1	Group # 2	Group # 3
Finding # 1 *	no./tot.	no./tot.	no./tot.
Finding # 2	no./tot.	no./tot.	no./tot.
Finding # 3	no./tot.	no./tot.	no./tot.

* i.e. Chronic Kidney Inflammation

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Counts of Tumors and Lesions by Individual Animal by Test Group

TESTS: Subchronic Oral .

Test Group

Animal Identification	Lesions		Tumors	
	Non-Neoplastic	Pre-Neoplastic	Benign	Malignant
________	________	________	____	______
________	________	________	____	______
Total	________	________	____	______

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Counts of Tumors and Lesions by Test Group

TESTS: Subchronic Oral

Group Identification	Number of Animals at Start of Test	Lesions				Tumors			
		Non-Neoplastic		Pre-Neoplastic		Benign		Malignant	
		Animals Affected	Total Count	Animals Affected	Total Count	Animals Affected	Total Count	Animals Affected	Total Count
______	______	______	___	______	___	______	___	______	___
______	______	______	___	______	___	______	___	______	___
______	______	______	___	______	___	______	___	______	___

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Number of Occurrance of Each Type of Tumor

TESTS: Subchronic Oral

Test Group Type of Tumor or Lesion	Group # 1	Group # 2	Group # 3
Type # 1*	___	___	___
Type # 2	___	___	___
Type # 3	___	___	___

* e.g. milignant tumor of the liver

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

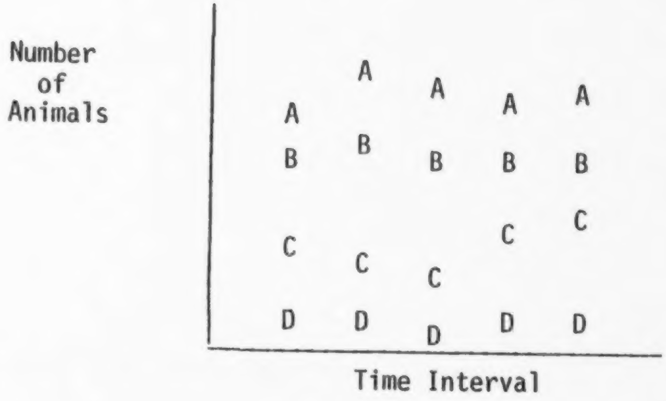
TITLE: Deaths of Animals with Tumors or Lesions by Time Interval by Test Group

TESTS: Subchronic Oral

Test Group
Tumor or Lesion*

A - Number of Animals Dying
B - Number of Animals in Which Tumor or Lesion was Found
C - Number of Animals in Which Tumor or Lesion Caused Death
D - Number of Animals in Which Tumor or Lesion Caused Moribundity

* e.g. pre-neoplastic liver lesion



APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Counts of Tumors or Lesions in Dead Animals by Test Group by Time Interval

TESTS: Subchronic Oral

Time Interval

Test Group Type of Tumor or Lesion	Group # 1	Group # 2	Group # 3
Type # 1*	—	—	—
Type # 2	—	—	—
Type # 3	—	—	—

* e.g. benign tumor of the brain

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Organ Weights by Individual Animal

TESTS: Subchronic Dermal, Subchronic Inhalation, Subchronic Oral

Group Identification	Animal Identification	Body Weight	Brain Weight	Organ	Organ Weight	Organ/Body Weight Ratio	Organ/Brain Weight Ratio
________	________	___	___	___	___	___	___
				___	___	___	___
				___	___	___	___
	________	___	___	___	___	___	___
				___	___	___	___
				___	___	___	___

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Average Organ Weights by Test Group

TESTS: Subchronic Inhalation, Subchronic Oral

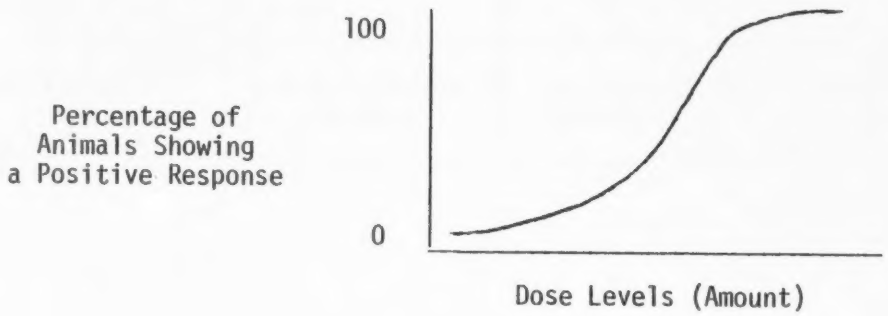
Group Identification	Body Weight		Organ	Organ Weight		Organ/Body Weight	
	Avg.	Std. dev.		Avg.	Std. dev.	Ratio	Std. dev.
________	___	___	___	___	___	___	___
			___	___	___	___	___
			___	___	___	___	___
________	___	___	___	___	___	___	___
			___	___	___	___	___
			___	___	___	___	___

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Dose Response Curve

TESTS: Acute Dermal, Acute Inhalation, Acute Oral, Subchronic Inhalation, Subchronic Oral, Reproduction



APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Testing and Evaluation Results by Individual Animal

TESTS: Subchronic Inhalation, Subchronic Oral, Reproduction

Group Identification	Animal Identification	Type of Test or Evaluation	Date Conducted	Results
______	______	______	______	______
		______	______	______
		______	______	______
	______	______	______	______
		______	______	______
		______	______	______

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Infectious Diseases and Treatment by Individual Animal

TESTS: Subchronic Inhalation, Subchronic Oral

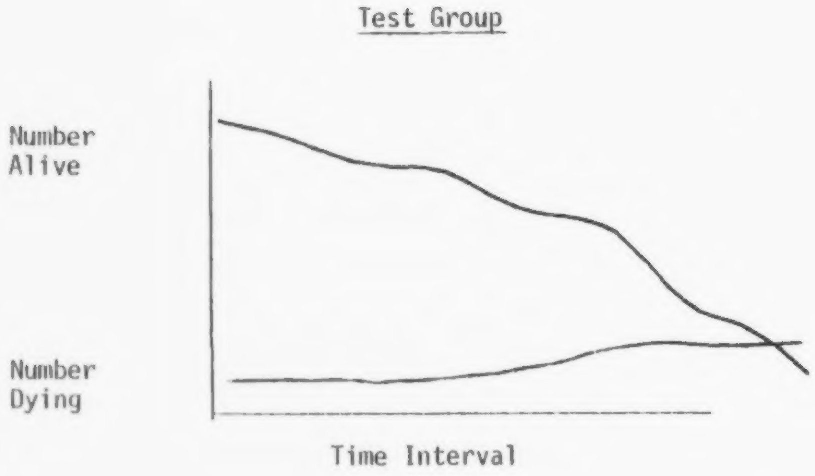
Group Identification	Animal Identification	First Observation		Disease Description	Treatment			Results
		Date	Time		Date	Time	Description	
________	________	__	__	______	__	__	______	____
					__	__	______	____
					__	__	______	____
		__	__	______	__	__	______	____
					__	__	______	____
	________	__	__	______	__	__	______	____
		__	__	______	__	__	______	____

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Number of Animals Alive and Dying for Each Time Interval by Test Group

TESTS: Subchronic Inhalation, Reproduction



APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Number of Animals Exposed and Dying by Group

TESTS: Acute Inhalation, Acute Oral

Group Identification	Number of Animals Exposed	Number of Animals Showing Signs of Toxicity	Number of Animals That Died	Time of Death After Dosing	
				Avg.	Std.dev.
________	____	___________	______	__	____
________	____	___________	______	__	____
________	____	___________	______	__	____

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Survival and Death Data by Time Interval by Test Group

TESTS: Subchronic Oral

Test Group

Animals / Time	Number Remaining Alive	Number of Deaths	Number of Deaths Other Than by Sacrifice	Number Sacrificed and Also Moribund at Time of Sacrifice
Interval # 1 *	____	___	____________	__________
Interval # 2	____	___	____________	__________
Interval # 3	____	___	____________	__________

* e.g. Week 1

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Age at Death and Time of Death by Individual Animal

TESTS: Acute Dermal, Acute Inhalation, Acute Oral, Subchronic Inhalation, Subchronic Oral, Reproduction

Group Identification	Age at Death		Animal Identification	Age		Death			Death by Sacrifice (y/n)	Moribund at Time of Sacrifice (y/n)	Necropsy	
	Avg.	Std. dev.		Start of Test	At Death	Week of Test	Date	Time			Date	Time
___	___	___	___	___	___	___	___	___	___	___	___	___
			___	___	___	___	___	___	___	___	___	___
			___	___	___	___	___	___	___	___	___	___
___	___	___	___	___	___	___	___	___	___	___	___	___
			___	___	___	___	___	___	___	___	___	___
			___	___	___	___	___	___	___	___	___	___

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Animals Not Subject to Necropsy

TESTS: Subchronic Inhalation, Subchronic Oral

Group Identification	Animal Identification	Manner in Which Necropsy or Histopathology Differed From Requirements	Reason For Variation

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Maternal Data by Individual Animal by Test Group

TESTS: Teratogenicity, Reproduction

Group Identification

Animal Identification	Age at Start of Test	Date of Confirmed Pregnancy	Date of Delivery	Weight At First Dose	Weight at Death	Gravid Uterine Weight	Body Weight Change	Observed Signs of Abortion or Premature Delivery

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Pregnancy Data by Test Group

TESTS: Teratogenicity

Group Identification	Animals Initially On Study	Animals Dying		Animals Pregnant		Maternal Body Weight Change	
		Number	%	Number	%	Average	Std. Dev.
________	______	____	___	____	___	____	______
________	______	____	___	____	___	____	______

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Fetal Data by Litter by Test Group

TESTS: Teratogenicity, Reproduction

Group Identification

Litter Identification	Live Fetuses		Live Fetal Weight		Sex		Dead or Resorbed Fetuses		Number of Implantations	Soft Tissue, Skeletal Abnormality	
	No.	%	Avg.	Std. dev.	M	F	No.	%		No.	%
________	___	___	___	___	_	_	___	___	________	___	___
________	___	___	___	___	_	_	___	___	________	___	___
________	___	___	___	___	_	_	___	___	________	___	___

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Anomaly·Data by Litter by Test Group

TESTS: Teratogenicity

Group Identification

Litter Identification	Number of Fetuses Examined by Necropsy	Fetuses Having Anomalies		Number of Fetuses Examined for Skeletal Anomalies	Fetuses Having Skeletal Anomalies	
		No.	%		No.	%
________	______	__	__	_______	__	__
________	______	__	__	_______	__	__
________	______	__	__	_______	__	__

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Litter and Abnormality Data by Test Group

TESTS: Reproduction

Group Identification	Length of Gestation		Reproductive Behavior Abnormalities		Offspring Per Litter						Behavioral Abnormalities in Nesting and Nursing	
					Total		Live		Dead			
	Avg.	Std. Dev.	No.	%	Avg.	Std. Dev.	Avg.	Std. Dev.	Avg.	Std. Dev.	No.	%
________	___	___	___	___	___	___	___	___	___	___	___	___
________	___	___	___	___	___	___	___	___	___	___	___	___
________	___	___	___	___	___	___	___	___	___	___	___	___

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Litter and Fetal Examination by Test Group

TESTS: Teratogenicity

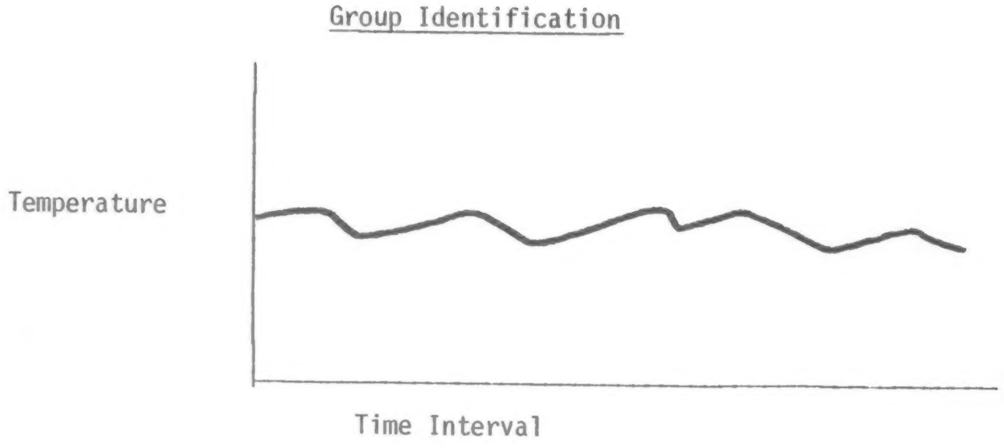
Group Identification	Number of Litters Examined	Implantations per Litter		Live Fetuses per Litter		Live Fetal Weight				Dead or Resorbed Fetuses		Fetuses Bearing Anomalies		Litters Having Anomalous Fetuses		Abnormal Fetuses Per Litter			
		Avg.	Std. Dev.	Avg.	Std. Dev.	Low	High	Avg.	Std. Dev.	%	Std. Dev.	No.	%	No.	%	Avg.	Std. Dev.	%	Std. Dev.
______	____	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
______	____	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Temperature Measurement by Time

TESTS: Acute Inhalation, Subchronic Inhalation

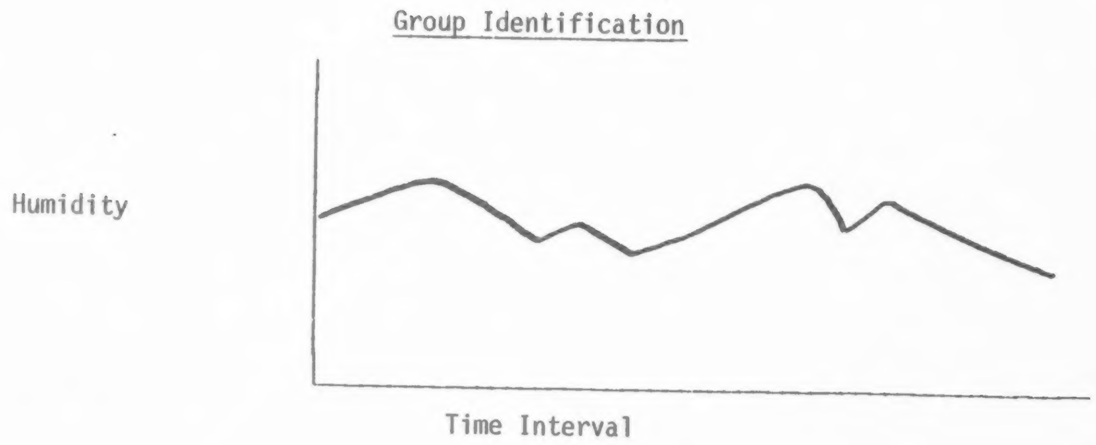


APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Humidity Measurement by Time

TESTS: Acute Inhalation, Subchronic Inhalation

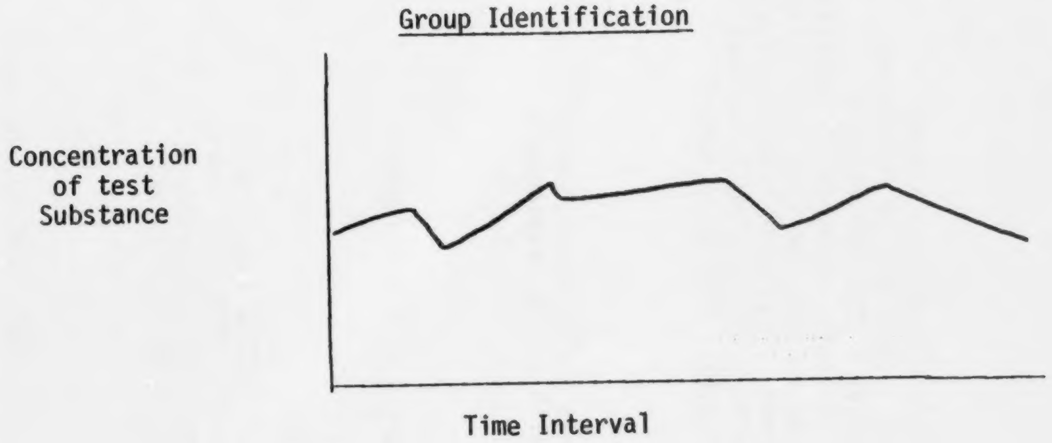


APPENDIX B

PROTOTYPE CTSS SUMMARY REPORTS

TITLE: Concentration of Test Substance at the Breathing Zone by Time

TESTS: Acute Inhalation, Subchronic Inhalation



APPENDIX C

CTSS INTERVIEWS

EPA:

Warren Muir - CTSS Development
Bob Beall - IRLG Testing Guidelines
Steve Heller - CTSS Development
Charles Colledge - Storage of Pesticide Test Data
Dr. Engler - Pesticide Test Data Evaluation
Bill Burnam - Pesticide Test Data Evaluation
Carl Morris - OTS Testing Guidelines
Morris Yaguda - CTSS Development

OSHA:

Phil Brown - CTSS Development
Pat Breslin - CTSS Development

FDA:

Al Gelberg - CTSS Development

CPSC:

Dr. Orzell - CTSS Development
Dr. Desmond - CTSS Development
Dr. Maisel - CTSS Development
Dr. Dyer - CTSS Development

NCI:

Sid Siegel - CBDS, TDMS Development

NCTR:

Larry Lawrence - TDMS Development, GLPs
Paul Brown - TDMS Development, GLPs

NLM:

Dr. Valley - TOX-TIPS, Toxicology Research Projects Directory
Don Hummel - TOX-TIPS, MEDLARS
Dr. Hoag - LADB
F. Gluckstein - LADB
R. Dozkocs - LADB

CEQ:

Larry Milask - UPGRADE Development

Manufacturing Chemists Association

George Ingle - CTSS Development

Synthetic Organic Chemical Manufacturers Association
Ronald Lang - CTSS Development

Litton Bionetics:

Al Butler - CTSS Data Collection and Submission

College of American Pathologists:

Janet Vokoun - Medical Classification & Nomenclature Systems

Regional Primate Research Center - Oregon:

Burt Coffin - SNOP, SNOMED Utilization

Smithsonian Science Information Exchange:

D. Elliot - CTSS General Inquiry Subsystem
S. Liebman - CTSS General Inquiry Subsystem

SDC Search Service

Sheryl Rosenthal - SSIE, NTIS

Lockheed Information Service

Mark Baer - SSIE, NTIS

APPENDIX D

IRLG TESTING GUIDELINE INFORMATION REQUIRED BY TYPE OF TEST

TYPE OF TEST / INFORMATION REQUIRED	ACUTE				SUB - CHRONIC			TERATOGENICITY	REPRODUCTION
	DERMAL	INHALATION	OCULAR	ORAL	DERMAL	INHALATION	ORAL		
1. Experiment Identification									
Laboratory performing test	X	X	X	X	X	X	X	X	X
Persons primarily responsible for test	X	X	X	X	X	X	X	X	X
Summary of test results and conclusions	X	X	X	X	X	X	X	X	X
Start date of test	X	X	X	X	X	X	X	X	X
Ending date of test	X	X	X	X	X	X	X	X	X
Experimental design and procedures	X	X	X	X	X	X	X	X	X
2. Test Substance Characteristics									
Chemical name	X	X	X	X	X	X	X	X	X
Molecular structure	X	X	X	X	X	X	X	X	X
Name of manufacturer	X	X		X					
Manufacturer's lot number	X	X		X					
Manufacturer's sample number	X	X		X					
PH	X	X		X					
Purity	X	X		X					
Storage method (mode)	X			X					
Stablility	X	X		X					
Chemical assays	X	X		X					
Composition (chemical name, quantity)	X	X		X					
Vapor pressure		X							
Particulate size of aerodynamic equivalence		X							
3. Animal/Grouping									
Species	X	X	X	X	X	X	X	X	X
Strain	X	X	X	X	X	X	X	X	X
Sex	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X
Age	X	X		X	X	X	X	X	X
Number of Animals	X	X	X	X	X	X	X	X	X
Number of animals per cage	X	X		X					

APPENDIX D (cont'd)

IRLG TESTING GUIDELINE INFORMATION REQUIRED BY TYPE OF TEST

TYPE OF TEST / INFORMATION REQUIRED	ACUTE				SUB - CHRONIC			TERATOGENICITY	REPRODUCTION
	DERMAL	INHALATION	OCULAR	ORAL	DERMAL	INHALATION	ORAL		
Weight ranges	X	X	X			X			
Unique animal identification number	X	X		X			X		
Role of each group (test, control, vehicle)	X	X		X	X	X	X	X	X
Control data (historical data on life span)	X	X		X					X
Supplier of animals	X	X		X					
Pretest conditioning	X	X		X					
Animal selection rationale	X	X		X	X	X	X	X	X
Randomization selection method used	X	X		X			X		
4. Dosage									
Dose Levels	X	X		X	X	X	X	X	X
Amount per dose	X	X	X	X	X				X
Concentration	X	X		X		X		X	X
Composition of dose						X			
Route of administration			X				X	X	X
Method of administration	X	X		X					
Frequency of administration	X	X		X	X	X		X	X
Vehicle used	X	X							
Exposure duration	X				X	X			
Selection rationale						X			X
Dilutents	X	X		X	X				
Suspending agents	X	X		X	X				
Emulsifiers	X	X		X	X				
LD 10-20%	X			X					
LD 50%	X			X					
LD 80-90%	X			X					
LC 10-20%		X		X					
LC 50%		X		X					
LC 80-90%		X		X					
5. Animal Observation									
Observation period	X	X	X	X	X	X	X	X	X
Time of death	X	X		X			X	X	X
Manner of death							X		X

APPENDIX D (cont'd)

IRLG TESTING GUIDELINE INFORMATION REQUIRED BY TYPE OF TEST

INFORMATION REQUIRED \ TYPE OF TEST	ACUTE				SUB - CHRONIC			TERATOGENICITY	REPRODUCTION
	DERMAL	INHALATION	OCULAR	ORAL	DERMAL	INHALATION	ORAL		
Method of observation	X	X		X					
Frequency of observation	X	X		X		X	X	X	X
Duration of observation		X		X					X
Time of observation	X	X	X		X	X	X	X	X
Weight Changes	X	X		X	X	X	X	X	X
Food Consumption						X	X	X	
Clinical Signs									
. Toxicity	X	X				X	X	X	X
. Skin & Fur	X	X		X	X				
. Eyes	X	X		X					
. Mucous membranes	X	X		X					
. Respiratory	X	X		X	X				
. Cardiovascular	X	X		X	X				
. Automatic nervous system	X	X		X					
. Central nervous system	X	X		X	X				
. Semato-motor activities	X	X		X					
. Tremors	X	X		X					
. Convulsions	X	X		X					
. Salivation	X	X		X					
. Draize Score	X	X		X					
. Diarrhea	X	X		X					
. Lethargy	X	X		X					
. Sleep	X	X		X					
. Coma	X	X		X					
. Lesions	X								
. Mortality					X	X	X	X	
. Moribundity						X	X		
. Ulceration of the cornea			X						
. Opacity of the cornea			X						
. Inflamation of the iris			X						
. Swelling of the eye lids			X						
. Excetory					X				
. Behavioral					X	X	X	X	
. Abortion								X	
. Premature delivery								X	
. Pregnancy								X	
. Nesting									X
. Nursing									X

APPENDIX D (cont'd)

IRLG TESTING GUIDELINE INFORMATION
REQUIRED BY TYPE OF TEST

TYPE OF TEST / INFORMATION REQUIRED	ACUTE				SUB - CHRONIC			TERATOGENICITY	REPRODUCTION
	DERMAL	INHALATION	OCULAR	ORAL	DERMAL	INHALATION	ORAL		
6. Facilities									
Structural requirements (cage)	X	X		X					
Space requirements (room)	X	X		X					
Cage conditions	X	X		X					
Bedding material	X	X	X	X					
Ambient temperature	X	X		X		X			
Ambient humidity	X	X		X		X			
Equipment design									
. Description		x				X			
. Rate of airflow		X				X			
7. Gross Necropsy									
Description of abnormality	X	X	X	X	X	X	X	X	X
Time between death and necropsy	X	X		X		X	X		
Organs to be examined									
. External surface							X		
. Orifices							X		
. Cranial cavity							X		
. Carcass							X		
. Abdominal viscera							X		
. Thoracic viscera							X		
. Cervical viscera							X		
. Tissues affected by test substance	X	X		X					
. Skin-untreated						X			
. Pananasal sinuses						X			
. Bone with marrow						X			
. Heart						X			
. Spleen	X			X		X			
. Adrenals						X			
. Pancreas						X			
. Nasal passages	X	X		X		X			
. Trachea	X	X		X		X			
. Bronchi	X	X		X		X			
. Lung	X	X		X		X			
. Stomach						X			
. Liver	X			X		X			

APPENDIX D (cont'd)

IRLG TESTING GUIDELINE INFORMATION REQUIRED BY TYPE OF TEST

TYPE OF TEST / INFORMATION REQUIRED	ACUTE				SUB - CHRONIC			TERATOGENICITY	REPRODUCTION
	DERMAL	INHALATION	OCULAR	ORAL	DERMAL	INHALATION	ORAL		
. Intestinal Track	X			X					
. Small intestine						X			
. Large intestine						X			
. Kidney	X			X		X			
. Urinary Bladder						X			
. Prostrate						X			
. Testes						X			
. Epididymis						X			
. Ovary						X			
. Uterus - corpus						X			
. Uterus - cervix						X			
. Spinal cord							X		
. Brain							X		
. Eyes						X			
. Reproductive organs									X
. All gross lesions						X			X
8. Microscopic necropsy									
Description of tumor or lesion							X		
Characterization of tumor or lesion							X		
Non-neoplagtic lesions							X		
Pre-neoplastic lesions							X		
Benign tumors							X		
Malignant tumors							X		
Caused death							X		
Caused moribundity							X		
Time first observed							X		
Tissues to be examined									
. Skin-untreated					X		X		
. Skin-treated					X				
. Skeletal muscle					X	X	X		
. Paranasal sinuses						X			
. Vertebrae							X		
. Sternum							X		
. Bone with marrow					X	X	X		
. Tibio-femoral joint							X		
. Heart					X	X	X		

APPENDIX D (cont'd)

IRLG TESTING GUIDELINE INFORMATION REQUIRED BY TYPE OF TEST

TYPE OF TEST / INFORMATION REQUIRED	ACUTE				SUB - CHRONIC			TERATOGENICITY	REPRODUCTION
	DERMAL	INHALATION	OCULAR	ORAL	DERMAL	INHALATION	ORAL		
. Aorta						X	X		
. Spleen					X	X	X		
. Thymus					X	X	X		
. Thyroid					X	X	X		
. Parathyroid					X	X	X		
. Adrenals					X	X	X		
. Pituitary						X	X		
. Pancreas					X	X	X		
. Lymph nodes					X	X	X		
. Trachea					X	X	X		
. Bronchi					X	X	X		
. Lung					X	X	X		
. Nasal passages						X			
. Salivary glands					X	X	X		
. Esophagus					X	X	X		
. Stomach					X	X	X		
. Liver					X	X	X		
. Small intestine					X	X	X		
. Large intestine					X	X	X		
. Kidney					X	X	X		
. Urinary bladder					X	X	X		
. Gonads							X		
. Prostrate					X	X	X		
. Testes					X	X	X		
. Ovary					X	X	X		
. Uterus - corpus					X	X	X		
. Uterus - cervix					X	X	X		
. Sciatic nerve						X	X		
. Spinal cord						X	X		
. Brain						X	X		
. Mammary glands					X	X	X		
. Eyes					X	X	X		
. Gall bladder						X	X		
. Reproductive organs									X
. All gross lesions					X		X		X
. Other target tissues					X	X	X		

9. Organ Weights

APPENDIX D (cont'd)

IRLG TESTING GUIDELINE INFORMATION REQUIRED BY TYPE OF TEST

INFORMATION REQUIRED / TYPE OF TEST	ACUTE				SUB - CHRONIC			TERATOGENICITY	REPRODUCTION
	DERMAL	INHALATION	OCULAR	ORAL	DERMAL	INHALATION	ORAL		
Body (carcass)					X				
Liver					X	X	X		
Kidney					X	X	X		
Spleen					X				
Heart					X	X	X		
Testes					X				
Ovaries					X				
Adrenals					X				
Lungs					X	X			
Brain					X	X	X		
Gonads							X		
Thyroid							X		
Parathyroid							X		
Pituitary							X		
Endocrin glands							X		
Date and time weighed						X			
10. Hematology									
Data conducted						X	X		
Hematocrit					X	X	X		
Hemaglobin					X	X	X		
Erythrocyte					X	X	X		
Total leucocyte Count					X	X	X		
Differential leucocyte count					X	X	X		
Reticulocyte count					X	X	X		
11. Blood Chemistry									
Data conducted						X	X		
Calcium					X		X		
Phosphorus					X		X		
Fasting glucose					X		X		
Blood urea nitrogen					X		X		
Total protein					X		X		
Hepatic enzymes					X				
Carbohydrate metabolism						X			
Liver function (SPGT, SCOT, SAP)						X	X		

APPENDIX D (cont'd)

IRLG TESTING GUIDELINE INFORMATION REQUIRED BY TYPE OF TEST

TYPE OF TEST / INFORMATION REQUIRED	ACUTE				SUB - CHRONIC			TERATOGENICITY	REPRODUCTION
	DERMAL	INHALATION	OCULAR	ORAL	DERMAL	INHALATION	ORAL		
Kidney function						X			
Electrolytes						X			
Lipids						X			
Hormones						X			
Blood cretinine							X		
Chloride							X		
Sodium							X		
Potassium							X		
Lactic dehydroginase							X		
Direct bilirubin							X		
Total bilirubin							X		
Albumin							X		
12. Litter Information									
Litter identification (unique number)								X	X
Uterus weight								X	
Litter weight								X	
Fetal resorption								X	X
Number of live fetuses								X	X
Number of stillborn fetuses								X	X
Number of implantations								X	
Litter size								X	X
Fetus weight								X	X
Date of confirmed pregnancy						X			
Date of delivery									X
Sex								X	
Skeletal anomalies								X	
Soft tissue anomalies								X	
13. Animal Disease and Treatment									
Nature and severity of disease							X		
Date disease first observed							X		
Nature of treatment							X		
Outcome of disease and treatment							X		
14. Miscellaneous Tests									

APPENDIX D (cont'd)

IRLG TESTING GUIDELINE INFORMATION REQUIRED BY TYPE OF TEST

TYPE OF TEST / INFORMATION REQUIRED	ACUTE				SUB - CHRONIC			TERATOGENICITY	REPRODUCTION
	DERMAL	INHALATION	OCULAR	ORAL	DERMAL	INHALATION	ORAL		
Urinalysis							X		
Cholinesterase						X	X		
Residue analysis							X		
Absorption							X		
Male spermatogenisis									X
15. Environmental Monitoring									
Rate of air flow		X				X			
Concentration of test substance		X				X			
Particulate concentrations		X				X			
Temperature		X				X			
Humidity		X				X			
Particulate size at breathing zone						X			
16. Statistical Analysis									
Statistical methods used	X	X					X	X	
Statistical standard deviations						X			
Rate of air flow						X			
Exposure level by theoretical concentration		X				X			
Exposure level by actual concentration		X				X			
Exposure level by temperature		X				X			
Exposure level by humidity		X				X			
Particulate size analysis		X				X			
Response data at exposure level by sex and time of death		X		X					
Body weight by time		X				X	X		
LC_t 50 (1 hr.)		X							
95% confidence level for LC_t 50		X							
Dose response curve		X				X	X		
LD 50				X					
95% confidence level for LD 50				X					
Time of death and necropsy by animal						X	X		
Hematological, biochemical and other tests by animal, sex, and dose level						X	X		
Food consumption by group by time						X	X		

APPENDIX D (cont'd)

IRLG TESTING GUIDELINE INFORMATION REQUIRED BY TYPE OF TEST

TYPE OF TEST / INFORMATION REQUIRED	ACUTE				SUB - CHRONIC		TERATOGENICITY	REPRODUCTION
	DERMAL	INHALATION	OCULAR	ORAL	DERMAL INHALATION	ORAL		
Weight by group by time					X	X		
Sacrificed animals by group by time					X	X		
Animals living by group by time					X	X		
Clinical observations by animal, test group, sex, or dose level, by time					X	X		
Disease and treatment by animal					X	X		
Gross necropsy by animal					X	X		X
Number of animals by gross abnormality					X	X		X
Organ weight, organ-body ratios by animal					X	X		
Organ weight, organ-boy ratios by group					X	X		
Microscopic lesion data by animal					X	X		
Microscopic lesion data by group					X	X		
Animals not subject to gross or microscopic necropsy					X	X		
Food consumption by animal by time						X		
Maternal data by animal							X	X
Maternal data by group							X	X
Litter data by test group								X